

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61F 2/06	A1	(11) International Publication Number: WO 99/44538 (43) International Publication Date: 10 September 1999 (10.09.99)
(21) International Application Number: PCT/US99/01790 (22) International Filing Date: 27 January 1999 (27.01.99) (30) Priority Data: 60/072,653 27 January 1998 (27.01.98) US (71) Applicant (for all designated States except US): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 22nd floor, 300 Lakeside Drive, Oakland, CA 94612-3550 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MURAYAMA, Yuichi [US/US]; 17352 Sunset Boulevard #404D, Pacific Palisades, CA 90272 (US). VINUELA, Fernando [US/US]; 16100 Sunset Boulevard #101, Pacific Palisades, CA 90272 (US). (74) Agent: DAWES, Daniel, L.; Myers, Dawes & Andras LLP, 6th floor, 650 Town Center Drive, Costa Mesa, CA 92626-1925 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: BIODEGRADABLE POLYMER/PROTEIN BASED COILS FOR INTRALUMENAL IMPLANTS (57) Abstract <p>This invention is an apparatus for forming a thrombus having a separable coil made at least in part of at least one bio-compatible, and adsorbable polymer or protein; and a placement device associated with the separable coil adapted to dispose the coil into a selected body lumen.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

BIODEGRADABLE POLYMER/PROTEIN BASED COILS FOR INTRALUMENAL IMPLANTS

YUICHI MURAYAMA and FERNANDO VIÑUELA

TECHNICAL FIELD

This invention is in the general field of surgical and endovascular interventional instruments and relates specially to intraluminal implants for occlusion of vessels or aneurysms.

BACKGROUND ART

Occlusion coils are used to occlude a site within a body lumen, such as a blood vessel, brain aneurysm, or vascular malformation. The coils are typically placed at a desired site within the lumen by means of a microcatheter. The coils are normally made of a radiopaque, biocompatible metals such as platinum, gold, or tungsten. In treating brain aneurysms the coils occlude the aneurysm by posing a physical barrier to blood flow and by promoting thrombus formation. The formation of the neo-endothelium and mature intra-aneurysmal thrombus is necessary prior to subsequent organization and scar formation that, in turn, yields a permanently occluded aneurysm.

In the presence of continued exposure of intra-aneurysmal coils to circulating blood, metallic coils are insufficiently thrombogenic to promote the establishment of firm and mature thrombus within the aneurysm. They do not appear to promote endothelialization across the wide neck of an aneurysm. Therefore, it is essential to perform tight packing of the aneurysm with coils for complete cure of the aneurysms. This may cause mass effect on adjacent the brain parenchyma or cranial nerves.

To accelerate wound healing in the aneurysm (i.e., promotion of scar formation) and to decrease mass effect of the aneurysm, "biologically active" bioabsorbable embolic material may be useful. Bioabsorbable polymers, such as polyglycolic acid and polyglycolic/poly-L-lactic acid copolymers, or bioabsorbable proteins, such as collagen and gelatins, have been used to make intraluminal implants. These bioabsorbable polymers or proteins are also used to provide a the drug delivery vehicle (such as for continuous local delivery of growth factors).

DISCLOSURE OF THE INVENTION

In the present invention a biodegradable polymer (or protein) coils are used to control thrombosis or accelerate wound healing of the brain aneurysms for which platinum coils sometimes have proven unsatisfactory.

Another aspect of the invention is a method of drug delivery system using biodegradable polymer (or proteins) in the combination with growth factors such as vascular endothelial growth factor (VEGF) or basic fibroblast growth factor (bFGF) which promote long lasting effect of the wound healing

These biodegradable coils are useful for treating giant brain aneurysms to prevent mass effect on the brain parenchyma or cranial nerves by shrinkage of scaring aneurysm.

MODES FOR CARRYING OUT THE INVENTION

The implants of the invention may be placed within body lumens, e.g., blood vessels, Fallopian tubes, etc., of any mammalian species, including humans. The implant coils are made of biocompatible and absorbable polymers or proteins. Examples of bioabsorbable polymers that have been used to make intraluminal implants are polyglycolic acid, poly-glycolic/poly-L-lactic acid copolymers, polycaprolactone, polyhydroxybutyrate /hydroxyvalerate copolymers, poly-L-lactide, polydioxanone, polycarbonates, and polyanhydrides. Examples of bioabsorbable proteins that have been used to make intraluminal implants are collagen, fibrinogen, fibronectin, vitronectin, laminin and gelatin. To achieve radiopacity, the bioabsorbable polymer coils may be coated with radiopaque materials such as tantalum or platinum. The bioabsorbable polymer or protein itself may be coated onto coils or wires of metals such as platinum or nitinol.

Preferred growth factors for use in the invention are the naturally occurring mammalian angiogenic growth such as vascular endothelial growth factors or basic fibroblast growth factors; mixtures of such growth factors may also be used if desired.

The biodegradable polymer coils of this invention can be placed within vessels using procedures well known in the art. Generally, the desired site within the vessel is accessed with a catheter. For small diameter tortuous vessels the catheter may be guided to site through the use of guide wires. Once the site has been reached the catheter lumen is cleared by removing guide wire. In the case of polymer occlusion coils, the coils are loaded by means of a pusher wire. The coils may be attached to the distal end of the pusher via a cleavable joint (e.g., a joint that is severable by heat, electrolysis, or other means) or a mechanical joint that permits the coil to be detached from the distal end of the pusher wire. Alternatively, the coils may be detached from the pusher wire, simply pushed through the catheter and expelled from the distal end of the catheter.

Details of specific embodiments and experimental results supporting the invention are provided in the following publications which are attached hereto and form a portion of this disclosure:

- 1) A new surface modification technique of platinum coils by ion implantation and protein coating: Use in intravascular treatment of brain aneurysms, Y.

Murayama et al., Nuclear Instruments and Methods in Physics Research B 127/128: 1015-18 (1997).

2) Cell Adhesion Control on GDC Surface by Ion Implantation: In Vitro and In Vivo Evaluation, Y. Murayama et al., Interventional Neuroradiology 3 (Suppl 1) 75-6 (abstract 72) (1997).

3) Ion Implantation and Protein Coating of Detachable Coils for Endovascular Treatment of Cerebral Aneurysms: Concepts and Preliminary Results in Swine Models, Y. Murayama et al., Neurosurgery 40(6): 1233-44 (1997).

Reprinted from

NIM B

Beam Interactions with Materials & Atoms

Nuclear Instruments and Methods in Physics Research B 127/128 (1997) 1015–1018

A new surface modification technique of platinum coils
by ion implantation and protein coating:
Use in intravascular treatment of brain aneurysms

Yuichi Murayama ^{a,b,*}, Yoshiaki Suzuki ^c, Fernando Viñuela ^a, Tarik F. Massoud ^a,
Huy M. Do ^a, Guido Guglielmi ^a, Masaya Iwaki ^c, Masami Kamio ^b, Toshiaki Abe ^b

^a Endovascular Therapy Service and Leo G. Rigler Radiological Research Center, UCLA Medical Center, Los Angeles, USA

^b Department of Neurosurgery, The Jikei University School of Medicine, Tokyo, Japan

^c The Institute of Physical and Chemical Research (RIKEN), Saitama, Japan



ELSEVIER

BEAM INTERACTIONS WITH MATERIALS AND ATOMS

Nuclear Instruments and Methods in Physics Research – Section B

Editors:

Prof. H.H. Andersen

The Niels Bohr Institute, Ørsted Laboratory,
Universitetsparken 5, DK 2100 Copenhagen Ø, Denmark
Tel. +45 35320482, fax +45 35320460, e-mail nimb@fys.ku.dk
Temporary address from April 1, 1997 to April 1, 1998:

Institut de Physique Nucléaire

F-91406 Orsay Cedex, France

Tel. +33 1 69156604, fax +33 1 69154507, e-mail nimb@fys.ku.dk

Dr. L.E. Rehn

Materials Science Division, Bldg 223, Rm S231, Argonne National Laboratory,
9700 South Cass Avenue, Argonne, IL 60439, USA

Tel. +1 630 2529297, fax +1 630 2523308, e-mail lynn_rehn@qmgate.anl.gov

Editorial Board:

P. BAUER (Linz)

K. BETHGE (Frankfurt)

T. DIAZ DE LA RUBIA (Livermore)

A. DUNLOP (Palaiseau)

R. ELLIMAN (Canberra)

G. FOTTI (Catania)

K.S. JONES (Gainesville)

W.N. LENNARD (Ontario)

M. MANNAMI (Kyoto)

A. NYLANDSTED LARSEN (Aarhus)

F. PÁSZTI (Budapest)

S.T. PICRAUX (Albuquerque)

D.B. POKER (Oak Ridge)

H.L. RAVN (Geneva)

K. SIEGBAHN (Uppsala)

M. SZYMONSKI (Cracow)

T. TOMBRELLO (Pasadena)

H. URBASSEK (Kaiserslautern)

A.E. WHITE (Murray Hill)

I. YAMADA (Kyoto)

ZHU Jieqing (Shanghai)

Aims and scope

Section B of Nuclear Instruments and Methods in Physics Research (NIM B) provides a special forum for the discussion of all aspects of the interaction of energetic beams with atoms, molecules and aggregate forms of matter. This includes ion beam analysis and ion beam modification of materials, as well as studies of the basic interaction mechanisms of importance for this work. The Editors invite submission of both theoretical and experimental papers of original research in this area.

Information for Advertisers

Advertising orders and enquiries can be sent to: International: Elsevier Science, Advertising Department, The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK; tel. +44 (0) 1865 843565, fax +44 (0) 1865 843976. USA, Canada: Weston Media Associates, Dan Lipner, P.O. Box 1110, Greens Farms, CT 06436-1110, USA; tel. +1 203 261 2500, fax +1 203 261 0101. Japan: Elsevier Science Japan, Marketing Services, 1-9-15 Higashi-Azabu, Minato-ku, Tokyo 106, Japan; tel. +81 3 5561 5033, fax +81 3 5561 5047.

Abstracted/indexed in:

Current Contents: Engineering, Technology and Applied Sciences;
EI Compendex Plus; Engineering Index; INSPEC; Physics Briefs.

Subscription information 1997

Volumes 121–133 of Nuclear Instruments and Methods in Physics Research - Section B (ISSN 0168-583X) are scheduled for publication. A combined subscription to NIM A volumes 384–401 and NIM B volumes 121–133 is available at a reduced rate.

Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis. Issues are sent by SAL (Surface Air Lifted) mail wherever this service is available. Airmail rates are available upon request. For orders, claims, product enquiries (no manuscript enquiries) please contact the Customer Support Department at the Regional Sales Office nearest to you:

New York: Elsevier Science, P.O. Box 945, New York, NY 10159-0945, USA; tel +1 212 633 3730 (Toll free number for North American customers: 1-888-4ES-INFO (437-4636)), fax +1 212 633 3680, e-mail usinfo-f@elsevier.com

Amsterdam: Elsevier Science, P.O. Box 211, 1000 AE Amsterdam, The Netherlands; tel +31 20 485 3757, fax +31 20 485 3432, e-mail nlinfo-f@elsevier.nl

Tokyo: Elsevier Science, 9-15, Higashi-Azabu 1-chome, Minato-ku, Tokyo 106, Japan; tel +81 3 5561 5033, fax +81 3 5561 5047, e-mail kyf04035@niftyserve.or.jp

Singapore: Elsevier Science, No. 1 Temasek Avenue, #17-01 Millenia Tower, Singapore 039192; tel +65 434 3727, fax +65 337 2230, e-mail asiainfo@elsevier.com.sg

Claims for issues not received should be made within six months of our publication (mailing) date.

US Mailing notice: Nuclear Instruments and Methods in Physics Research – Section B (ISSN 0168-583X) is published semi-monthly (for five months of the year), monthly from August to December, three times a month in May, and four times in April, by Elsevier Science B.V., Molenwerf 1, P.O. Box 211, 1000 AE Amsterdam, The Netherlands. Annual subscription price in the USA is US\$ 6396 (valid in North, Central and South America only), including air speed delivery. Periodicals postage paid at Jamaica, NY 11431.

USA Postmasters: Send address changes to Nuclear Instruments and Methods in Physics Research – Section B, Publications Expediting, Inc., 200 Meacham Avenue, Elmont, NY 11003. Airfreight and mailing in the USA by Publications Expediting Inc.

© The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

Printed in The Netherlands



North-Holland, an imprint of Elsevier Science



A new surface modification technique of platinum coils by ion implantation and protein coating: Use in intravascular treatment of brain aneurysms

Yuichi Murayama ^{a,b,*}, Yoshiaki Suzuki ^c, Fernando Viñuela ^a, Tarik F. Massoud ^a,
Huy M. Do ^a, Guido Guglielmi ^a, Masaya Iwaki ^c, Masami Kamio ^b, Toshiaki Abe ^b

^a Endovascular Therapy Service and Leo G. Rigler Radiological Research Center, UCLA Medical Center, Los Angeles, USA

^b Department of Neurosurgery, The Jikei University School of Medicine, Tokyo, Japan

^c The Institute of Physical and Chemical Research (RIKEN), Saitama, Japan

Abstract

Ion implantation and protein-coatings were utilized to alter the surface properties (thrombogenicity, endothelial cellular migration and adhesion) of microcoils (GDCs) for intravascular treatment of brain aneurysms. These modified coils were compared with standard GDCs in the treatment of experimental swine aneurysms. Improved cellular adhesion and proliferation was observed with use of the modified coils. The results of this preliminary investigation indicate that future application of this technology may provide early wound healing at the necks of embolized wide-necked brain aneurysms.

Introduction

Brain aneurysms are the commonest cause of non-traumatic subarachnoid hemorrhage (SAH) which is a significant life-threatening disease in adults. Annually in North America, the rupture of saccular aneurysms accounts for 25000 new cases of SAH. Microsurgical clipping of an aneurysm has been considered the gold standard for the treatment of this disease. Recently, intravascular treatment of aneurysms has become an accepted alternative technique. With the availability of microcatheters capable of crossing the intracranial circulation it has become possible to obliterate an aneurysm by filling it with soft platinum detachable coils (Guglielmi Detachable Coils; GDC) [2]. Use of the GDC system allows controlled delivery and detachment of platinum coils within an aneurysm. However, the anatomical results of obliteration of either wide-necked (neck size ≥ 4 mm) or giant aneurysms using GDCs are generally unsatisfactory [3,4]. The reasons for these incomplete anatomical results in wide-necked lesions include aneurysmal recanalization and the potential for distal migration of detached coils. Early intravascular re-endothelialization at the necks of aneurysms and the acceleration of "wound healing" in the aneurysmal sac and some are potential solutions that may help achieve successful permanent cure of these types of aneurysms. Some

investigators have applied simple protein coatings on GDCs to enhance their thrombogenicity and wound healing properties [5]. However, intravascular embolization techniques generally make use of small-diametered microcatheters for delivery of these coils. Simple protein coating, therefore, results in the problem of increasing the diameter of these coils which, in turn, causes them to stick within the lumen of a microcatheter during coil delivery. We utilized ion implantation technology in combination with extracellular matrix protein coatings to alter the surface properties of GDCs without increasing the diameter of the coils. It was hypothesized that use of these modified coils may be useful in achieving a complete obliteration of aneurysms possessing wide necks by acceleration of re-endothelialization and "wound healing". The purpose of this preliminary study was to investigate the potential effectiveness of modified ion-implanted protein-coated GDCs in intravascular treatment of experimental wide-necked aneurysms in swine.

2. Experimental

2.1. Ion implantation process

GDCs of sizes 8×40 , 8×20 , 6×20 , 5×15 (coil diameter [mm] \times length [cm]) were coated with either fibrinogen (human fibrinogen, 20 mg/ml; Midoriuji, Osaka, Japan), or vitronectin (bovine plasma vitronectin, 0.1

* Corresponding author. Fax: +1-310-206-5958

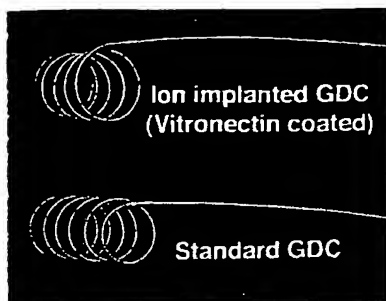


Fig. 1. Macroscopic appearance of a standard GDC and an ion-implemented protein-coated GDC. Note no increasing the diameter of protein coated-ion implanted coils (same diameter microcatheters were used).

mg/ml; KOKEN, Tokyo, Japan). The coating method entailed simply dipping the coil into the protein solutions. These coils underwent Ne^+ implantation with a fluence of 1×10^{15} ions/cm² at an energy of 150 keV (Fig. 1). The prototype target chamber was developed to achieve uniform implantation for GDCs. The beam current density used was lower than 0.5 $\mu\text{A}/\text{cm}^2$ to prevent an increase of the specimen temperature.

2.2. Assessment of GDCs in experimental aneurysms

2.2.1. Aneurysm construction

Six Red Duroc swine were used in experimental studies. Under general anesthesia, twelve experimental aneurysms were constructed microsurgically in bilateral common carotid arteries of six swine (Fig. 2). The right external jugular vein was isolated and divided into two segments to make two aneurysms. The right common carotid artery was exposed and a seven mm length arteriotomy was performed. A venoarterial end-to-side anastomosis was made using 7-0 prolene. The second aneurysm

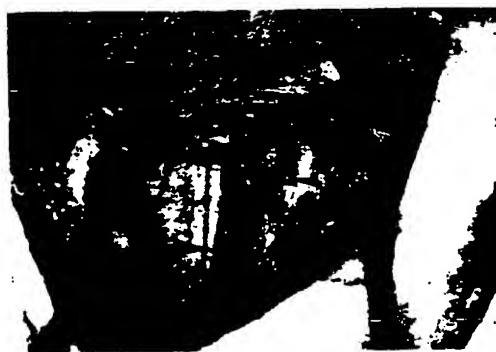


Fig. 2. Macroscopic appearance of surgically created experimental aneurysm in swine. Straight arrows: common carotid artery. Curved arrow: fabricated experimental aneurysm.

was constructed on the left common carotid artery. The aneurysms were almost all of equal size, ranging from 8 mm to 10 mm.

2.2.2. Aneurysm embolization

All endovascular treatments were undertaken in aneurysms immediately after their construction. Bilateral

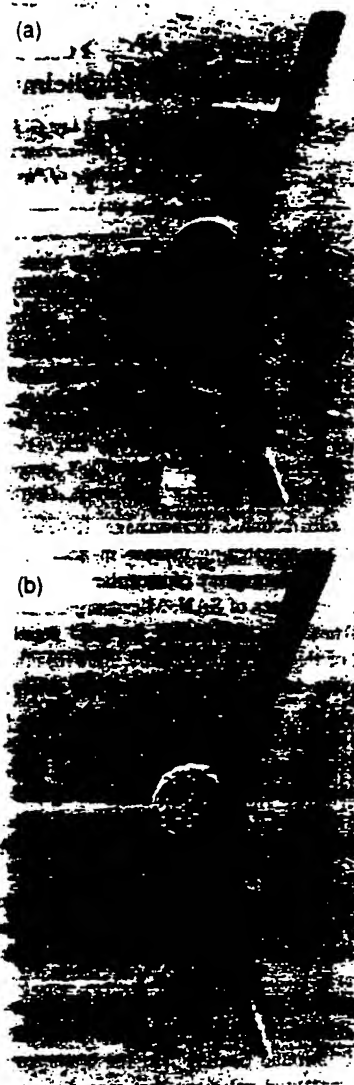


Fig. 3. Before embolization: Angiograms of the experimental aneurysms created on the common carotid arteries (a). Straight arrows: common carotid artery. Curved arrow: experimental aneurysm. After embolization: Angiograms of occluded aneurysms using ion-implanted GDCs (b). Arrows: packed aneurysm with platinum coils.

aneurysms were embolized in each animal, and the relative differences in wound healing between treatments using ion-implanted and standard GDCs were evaluated.

Via transfemoral route, a selective common carotid arteriogram was performed (Fig. 3a). A bolus 3000 U of heparin was injected to prevent thrombosis during the procedure. Next, a 2.1-F microcatheter was advanced coaxially through the guiding catheter and the tip of the microcatheter was positioned into the center of the aneurysm sac. The aneurysms were embolized with standard GDCs on one side and with protein-coated ion-implanted GDCs on the contralateral side (Fig. 3b).

Diagnostic angiography was performed and the animals were sacrificed at day 14 after coil placement. The aneurysmal orifice (as viewed from within the artery lumen) was observed macroscopically. The largest dimension of the orifice (OF) and the thick white fibrous membrane (FM) which covered the orifice were measured as the FM to OF ratio (and recorded as the $FM/OF \times 100\%$). $n = 6$ for standard group; $n = 6$ for ion-implanted protein-coated group [$n = 4$ with vitronectin, $n = 2$ with fibrinogen] (n is the number of the sample). In this study, particular attention was paid to the promotion of fibrous membrane coverage over the aneurysm orifice as a measure of wound healing acceleration. Statistical analysis of the FM to OF ratio was performed using a student *t*-test (paired 2-tail). Results were considered significant at $P < .05$ and reported as the mean \pm SD.

3. Results and discussion

3.1. Macroscopic and microscopic findings

On specimens examined 14 d after embolization, greater re-endothelialization and wound healing at the neck of the aneurysm were observed macroscopically with ion-implanted GDC. Whereas only a thin layer covered the standard GDC surfaces (Fig. 4a, 4b). The mean FM to OF ratio was $69.3 \pm 9.7\%$ for the ion-implanted GDC group and $40.8 \pm 17.7\%$ for the standard GDC group ($P = .0085$; Fig. 5).

3.2. Intravascular aneurysm treatment

The development of intravascular embolization techniques has provided a new alternative for the treatment of brain aneurysms. The development of Guglielmi detachable coils has contributed especially to improvements in clinical outcome and to reduced complications. This technique is based on the theory of intra-aneurysmal electrothrombus formation to prevent rupture of the aneurysm. However, complete occlusion is achieved in 85% of small-necked aneurysms (neck < 4 mm), and 15% of wide-necked aneurysms (neck size ≥ 4 mm) [4]. Furthermore, some recent clinical studies have shown recanaliza-

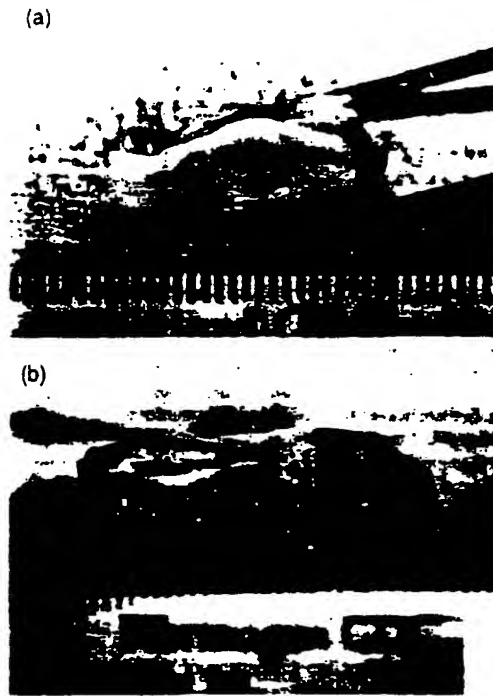


Fig. 4. Macrographic appearances of aneurysm orifices 14 days after treatment, using: standard GDCs (a), fibrinogen-coated ion-implanted GDCs (b).

tion of aneurysms that were supposedly satisfactorily treated. One of the reasons for these incomplete anatomical results is coil compaction due to effects of blood flow dynamics. To prevent recanalization, intimal scar formation across the neck of the aneurysm is essential. However, Mizoi et al. [6] and Molyneux et al. [7] have recently reported autopsy and surgical studies of patients treated by GDCs. The histological studies of the embolized aneurysms showed that the orifices of the aneurysms were not endothelialized and the aneurysm sacs were filled with unorganized thrombus. These results suggest that acceleration of wound healing and re-endothelialization are necessary prerequisites for complete cure of brain aneurysms when treated by endovascular means.

3.3. Ion implantation for platinum coils

Protein coating of platinum coils seems to be effective in enhancing thrombogenicity and wound healing [5]. However, simple protein coating results in the problem of increasing the diameter of these coils. Furthermore, weakly coated proteins may wash off by the high flow of arterial blood and may be a potential source of distal thromboemboli. Thus, strong fixation of the proteins onto the platinum surface and minimal increase in the diameter of the

VI. APPLICATIONS

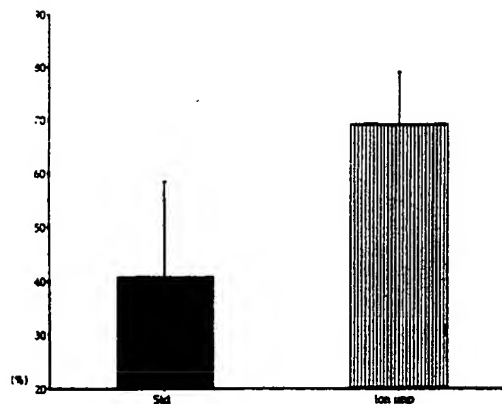


Fig. 5. Statistical analysis of FM to OF ratio for treated aneurysms at day 14. Standard GDC group: $40.8 \pm 17.7\%$, ion-implanted GDC group: $69.3 \pm 9.7\%$ ($p = 0.0085$, paired 2-tail).

treated platinum coils are necessary to address these limitations. Ion implantation is an effective method to immobilize proteins onto a platinum surface, without increasing their diameter significantly.

Suzuki et al. [8-10] recently applied ion implantation technology to alter the properties of protein-coated poly-

mer surfaces in order to achieve blood biocompatibility. The ideal combination of ion species and proteins, and the optimal intensity of ions and energy are still under investigation. In the present study, we demonstrated acceleration of wound healing at the necks of experimental aneurysms which were treated by ion-implanted protein-coated GDCs. However, development of a uniform ion implantation system is necessary for clinical application of this novel technique. Further utilization of ion implantation may open up new possibilities of achieving biocompatible materials in the medical field.

References

- [1] G. Guglielmi et al., *J. Neurosurg.* 75 (1991) 1.
- [2] G. Guglielmi et al., *J. Neurosurgery* 75 (1991) 8.
- [3] G. Guglielmi et al., *J. Neurosurgery* 77 (1992) 515.
- [4] A.F. Zubillaga et al., *AJNR Am. J. Neuroradiol.* 15 (1994) 815.
- [5] R.C. Dawson et al., *J. Neurosurgery* 36 (1995) 133.
- [6] K. Mizoi et al., *J. Neurosurgery* 39 (1996) 165.
- [7] A.J. Molyneux et al., *J. Neurosurgery* 83 (1995) 129.
- [8] Y. Suzuki et al., *Nucl. Instr. and Meth. B* 59/60 (1991) 698.
- [9] Y. Suzuki et al., *Nucl. Instr. and Meth. B* 65 (1992) 142.
- [10] Y. Suzuki et al., *Nucl. Instr. and Meth. B* 91 (1994) 588.

BEAM INTERACTIONS WITH MATERIALS AND ATOMS

Nuclear Instruments and Methods in Physics Research – Section B

Instructions to Authors

Submission of papers

Contributions should be submitted to one of the Editors (see inside front cover). It is suggested that manuscripts originating from Europe, India, The Middle East and Africa be sent to Prof. H.H. Andersen, and from The Americas, The Far East and Australasia, to Dr. L.E. Rehn.

Manuscript and figures should be submitted in duplicate, with one set of good quality figure material for production of the printed figures. If possible, please submit also an electronic version of your contribution on diskette.

Short contributions of less than 1500 words and not subdivided into sections may be published as Letters to the Editor in a shorter time than regular articles as the proofs will normally be corrected by the Publisher.

Submission of a manuscript implies that it is not being considered for publication elsewhere and that the authors have obtained the necessary authority for publication.

Manuscript preparation

Manuscripts should be written in good English. They should be typed throughout with double line spacing and wide margins on numbered, single column pages. See notes opposite on electronic manuscripts.

Structure. Please adhere to the following order of presentation: article title, author(s), affiliations, abstract, PACS codes and keywords, main text, acknowledgements, appendices, references, figure captions, tables.

Corresponding author. The name, full postal address, telephone and fax numbers and e-mail address of the corresponding author should be given on the first page.

Classification codes/keywords. Please supply one to four classification codes (PACS and/or MSC), and up to six keywords of your own choice that describe the content of your article in more detail.

References to other publications should be numbered consecutively within square brackets and listed together at the end of the text. In the case of multiple authorship all authors should be listed in the references; only in case of more than ten authors is the first author et al. acceptable.

Illustrations

The Publisher requires a set of good quality drawings and original photographs to produce the printed figures.

Line drawings should be 1.5–3 times larger than the printed size; the height of letters and numbers should, after reduction, fall within the range 1.2–2.4 mm. Do not use too narrow pen widths for machine-plotted graphs. Shaded areas should be shown by means of cross-hatching or a matrix of dots, rather than a continuous grey wash.

Photographs should not already be screened (overprinted with the point matrix used by printers). The top side of a photograph should be marked if necessary.

Colour figures can be printed in colour when this is essential to the presentation. Authors will be charged for colour reproduction. Further information can be obtained from the Publisher.

After acceptance

Notification. You will be notified by the Editor of the acceptance of your contribution, and invited to send an electronic file of the accepted version to the Publisher, if this is not yet available. After acceptance any correspondence should be addressed to the Publisher at the coordinates below.

Page proofs are sent out to the Author in order to check that no undetected errors have arisen in the typesetting or file conversion process. In the proofs only typesetting errors may be corrected. No changes in, or additions to, the accepted paper will be accepted.

Copyright transfer. In the course of the production process the authors will be asked to transfer the copyright of the article to the publisher. This transfer will ensure the widest possible dissemination of information.

Electronic manuscripts

If possible, an electronic version of the manuscript should be submitted on a diskette together with the hard copies of the text and figures, or should be sent (after acceptance) by e-mail or on a diskette to the Publisher. It is the responsibility of the Author to ensure that the electronic version exactly matches the hard copy. No deviations from the version accepted for publication are permissible without the prior and explicit approval by the Editor. Such changes should be clearly indicated on an accompanying print-out of the file.

LaTeX articles and articles prepared with any of the well known word processors can be handled by the Publisher. Further information can be obtained from the Publisher.

Author benefits

No page charges. Publishing in Nuclear Instruments and Methods in Physics Research – Section B is free.

Free offprints. The corresponding author will receive 50 offprints free of charge. An offprint order form will be supplied by the publisher for ordering any additional paid offprints.

Discount. Contributors to Elsevier Science journals are entitled to a 30% discount on all Elsevier Science books.

Correspondence with the Publisher

After acceptance of an article any correspondence should be addressed to Elsevier Science B.V., NIM-B, P.O. Box 2759, 1000 CT Amsterdam, The Netherlands
Tel. +31 20 485 2500, fax +31 20 485 2431
e-mail nimb-j@elsevier.nl



North-Holland, an imprint of Elsevier Science

INTERVENTIONAL NEURORADIOLOGY

Journal of Peritherapeutic Neuroradiology, Surgical Procedures and Related Neurosciences
Official Journal of the World Federation of Interventional and Therapeutic Neuroradiology
Official Journal of the Japanese Society for Intravascular Neurosurgery

ASITN-WFITN 1997

Scientific Conference

Contents

Welcoming Address	3
ASITN - WFITN Executive and Scientific Committees	4
General Information	5
Future Meetings	7
Social Program	8
Schedule of Events	10
Acknowledgements	11
Educational Objectives	12
New York Marriott Marquis Hotel - Floor Plan	13
Scientific Program	14
Invited Speakers	22
Scientific Exhibits	25
Scientific Papers	35
Scientific Posters	121
ASITN Members	157
WFITN Members	149
Author Index	161
JSIN Bulletin	165
Instructions to Authors	168

ninety five patients with metastatic lesions to the spinal column, with good devascularization in the preoperative group and good palliation of pain in nearly all patients.

Conclusion: Endovascular therapy is a safe and effective method of treating metastatic spinal column tumors. In patients with no hope of cure for their tumors, palliation of symptoms can be achieved with minimal risk by using cytotoxic agents such as EtOH, and/or NBCA, and the vascular pedicles can be preserved, allowing for future therapy following the inevitable progression of the disease. Additionally, presurgical embolization with PVA, or other particles soaked in EtOH reduces operative blood loss and provides a bloodless field, which facilitates tumor removal allowing more aggressive surgical options. The use of both motor and sensory evoked potentials combined with preembolization provocative testing with lidocaine and/or sodium amytal further reduces the risks associated with these procedures, making embolization both a safe and effective adjunctive therapy in the treatment of metastatic lesions to the spinal column.

Key words: spine, tumor

71

START TIME 8:48 A END TIME 8:53 A

Combined Pre-operative Trans-arterial and Trans-venous Embolization of Jugular Fossa Paragangliomas

Jacobs J.M., Shelton C., Thompson B.G.
University of Utah Health Sciences Center;
Salt Lake City, UT

Purpose: The purpose of this presentation is to illustrate the technical aspects and benefits of combined trans-arterial and trans-venous embolization of jugular, skull base paragangliomas prior to surgical resection.

Methods: We will present five cases in which the combined trans-arterial and trans-venous approach was used in the pre-operative embolization of jugular, skull base paragangliomas. In each instance the femoral arterial route was used to perform angiography to evaluate the arterial supply and venous drainage of the tumor and adjacent structures. Trans-arterial embolization was performed of the ascending pharyngeal artery and/or the occipital artery in the customary fashion using polyvinyl alcohol particles suspended in contrast material. Then, trans-venous embolization was performed by placing a guide catheter into the contra-lateral jugular bulb from the femoral route. A micro-catheter was then advanced retrograde through the contra-lateral inferior petrosal sinus, across the mid-line into the ipsilateral in-

ferior petrosal sinus. The micro-catheter was then positioned into the distal ipsilateral inferior petrosal sinus where coil embolization was performed. The venous guide catheter and micro-catheter were then positioned into the ipsilateral condylar vein(s) where coil embolization was also performed. Surgical resection was then performed by the Neurosurgery and Neuro-otology team via a trans-petrosal approached with extra-dural or extra-dural/intra-dural exposure depending on the extent of the tumor.

Results: We will discuss the technical aspects of both the embolization and resection of these tumors and describe the benefits of the combined intra-arterial and intra-venous embolizations.

Key words: percutaneous techniques, tumor

72

START TIME 11:00 A END TIME 11:05 A

Cell Adhesion Control on GDC Surface by Ion Implantation: In Vitro and In Vivo Evaluation

Murayama Y., Viñuela F., Suzuki F.,
Ulhoa A., Akiba Y., Guglielmi G., Iwaki M.,
Kaibara M., Abe T.
UCLA, Los Angeles, CA

Purpose: To evaluate the value of ion implantation technology when applied to GDC treatment of aneurysm by: 1) In vitro evaluation of the effects of ion implantation and protein coating to promote endothelial migration and adhesion in endothelial cell cultures on non-cell adhesive polymers (segmental polyurethane: SPU) or platinum plates. 2) In vivo treatment of surgically created wide-necked aneurysms in swine with angiographic and histopathological follow-ups. Special attention was paid to coil compaction, aneurysm remnant formation, and histology in the neck interface after use of modified GDCs.

Methods: 1) In Vitro Study: The surface of SPU or platinum dishes were divided into four areas to be subjected to four different conditions. Area 1: ion implantation without protein coating. Area 2: protein coating without ion implantation. Area 3: protein coating with ion implantation and Area 4 was defined as the remaining bare SPU/or platinum surface as control. Areas 2 and 3 were coated with type I collagen or fibrinogen. He+ or Ne+ implantation were performed on area 1 and Area 3 with fluences of 1×10^{14} or 1×10^{15} at an energy of 150 keV at room temperature. Bovine endothelial cells ($2-2.5 \times 10^4$ cells in 1 ml) were suspended in medium supplemented with 10% FBS on the SPU or platinum plates. During incubation periods of 2 to 7 days, the extent of cellular adhesion and migration were determined with a

phase contrast microscope and scanning electron microscope (SEM). Five days after cell seeding, the resistance to detachment of cells was evaluated by trypsin treatment. The cell detachment from SPL[®] platinum surface was microscopically counted.

2) Chronic Experimental Aneurysm Study: GDCs were coated with either type I collagen, fibronectin, vitronectin, laminin or fibrinogen. Ion implantation was then performed on these protein-coated GDCs. Forty experimental aneurysms were constructed microsurgically in bilateral common carotid arteries of 19 swine. The aneurysms were embolized with standard GDCs or with ion-implanted protein-coated GDCs. The animals were sacrificed at day 14 after coil placement. The aneurysmal orifice was observed macroscopically and histopathological study was performed.

Results: In vitro study showed that endothelial cell adhesion/proliferation was accelerated by ion implantation. Five days after cell seeding, both simple collagen coated surface and collagen coated ion implanted surface showed endothelial adhesion and proliferation. Following Trypsin treatment, the cells did not detached from the ion implanted collagen coated surface. To the contrary, the cells were detached from the non-ion implanted collagen coated surface. It was confirmed that the strength of cell attachment was modified by ion implantation. On specimens examined 14 days post-embolization, greater fibrous tissue coverage at the neck of the aneurysm were observed. Light microscopy showed that well organized fibrous tissue bridged the aneurysmal neck when using ion implanted GDCs, whereas only a fibrin-like thin layer covered the standard GDC surfaces.

Conclusion: These in vitro and in vivo study indicate that ion implantation combined with protein coating of GDCs improved cellular adhesion/proliferation. This technology may provide improvement of longterm anatomical and clinical outcome of cerebral aneurysms.

Key words: devices, embolic materials, aneurysm, experimental

73

START TIME 11:06 A END TIME 11:11 A

Development of Platinum Microcoils Containing Biochemically Active Macromolecules (VEGF)

Tsuura M., Terada T., Uematsu Y., Yokote H., Nakai K., Itakura T., Ogawa A.*

Dept. of Neurological Surgery, Wakayama Medical College; Wakayama, Japan

* *Kaneka Medix Corporation; Kanagawa, Japan*

Purpose: Polyvinyl alcohol (PVA) has been used as an implantable carrier for sustained delivery of

macromolecules in animal tissues. To release proteins or macromolecules continuously around platinum coils for endovascular treatment, we have developed new platinum coils with a polyvinyl alcohol (PVA) core which can contain various biochemically active substances.

Methods: New platinum coils have central cores made from a mixture of casting solution of PVA and biochemically active macromolecules. This PVA core is expected to release the macromolecules around the platinum coil. Platinum coils with a central core made from (1) PVA only and (2) PVA and vascular endothelial growth factor (VEGF), were placed on cultured human aortic endothelial cells. Surface of platinum coils cocultured with endothelial cells was observed under phase-contrast microscope.

Results: Cultured endothelial cells began to cover the surface of VEGF-containing platinum coils after 4 days and covered the entire coil surface 7 days after placement. VEGF-containing coils tend to be covered by cultured human aortic endothelial cells earlier than platinum coils without VEGF.

Conclusion: VEGF-containing coils seem to enhance early and rapid covering of endothelial cells after coil placement. Our platinum coils with a core of PVA for sustained release of proteins or macromolecules may be useful for embolization of cerebral aneurysms.

References

- 1 Langer R, Folkman J: Polymers for the sustained release of proteins and other macromolecules. *Nature* 263: 797-800, 1976.
- 2 Fejardo LF, Kowalski J et Al: Methods in laboratory investigation. The disc angiogenesis system. *Lab Invest* 58: 718-724, 1988.

Key words: devices, embolic materials, aneurysm, experimental

74

START TIME 11:12 A END TIME 11:17 A

Immediately Electrically Detachable Coil (IEDC) for Aneurysm Treatment

Murao K., Taki W., Sadato A., Nakahara I., Sakai N., Waga S.*

*Department of Neurosurgery, Kyoto University School of Medicine, * Department of Neurosurgery, Mie University School of Medicine; Tsu, Mie Japan*

Purpose: We developed endovascular coils that are instantly detached by high-frequency electrical current, and have obtained good results with IEDC in animal experiments. On the basis of the results, we applied these devices to clinical cases.

Methods: IEDC has a polyvinyl alcohol (PVA) rod at the junction of a soft circular platinum coil and the delivery guidewire. The diameter of the

EXPERIMENTAL STUDIES

Ion Implantation and Protein Coating of Detachable Coils for Endovascular Treatment of Cerebral Aneurysms: Concepts and Preliminary Results in Swine Models

Yuichi Murayama, M.D., Fernando Viñuela, M.D.,
Yoshiaki Suzuki, Ph.D., Huy M. Do, M.D.,
Tarik F. Massoud, M.D., Guido Guglielmi, M.D.,
Cheng Ji, M.D., Masaya Iwaki, Ph.D.,
Masahiro Kusakabe, Ph.D., Masami Kamio, M.D.,
Toshiaki Abe, M.D.

Endovascular Therapy Service and Leo G. Rigler Radiological Research Center
(YM, FV, HMD, TFM, GG, CI), University of California, Los Angeles, Medical Center,
Los Angeles, California; The Institute of Physical and Chemical Research (RIKEN)
(YS, MI), Saitama, Japan; Department of Neurosurgery (YM, MKa, TA),
The Jikei University School of Medicine, Tokyo, Japan; and Corporate Research
Laboratory (MKu), SONY Corporation, Tokyo, Japan

OBJECTIVE: Complete anatomic obliteration remains difficult to achieve with endovascular treatment of wide-necked aneurysms using Guglielmi detachable platinum coils (GDCs). Ion implantation is a physicochemical surface modification process resulting from the impingement of a high-energy ion beam. Ion implantation and protein coating were used to alter the surface properties (thrombogenicity, endothelial cellular migration, and adhesion) of GDCs. These modified coils were compared with standard GDCs in the treatment of experimental swine aneurysms.

METHODS: In an initial study, straight platinum coils were used to compare the acute thrombogenicity of standard and modified coils. Modified coils were coated with albumin, fibronectin, or collagen and underwent Ne^+ ion implantation at a dose of 1×10^{15} ions/cm² and an energy of 150 keV. Coils were placed in common iliac arteries of 17 swine for 1 hour, to evaluate their acute interactions with circulating blood. In a second study, GDCs were used to treat 34 aneurysms in an additional 17 swine. GDCs were coated with fibronectin, albumin, collagen, laminin, fibrinogen, or vitronectin and then implanted with ions as described above. Bilateral experimental swine aneurysms were embolized with standard GDCs on one side and with ion-implanted, protein-coated GDCs on the other side. The necks of aneurysms were evaluated macroscopically at autopsy, by using post-treatment Day 14 specimens. The dimensions of the orifice and the white fibrous membrane that covered the orifice were measured as the fibrous membrane to orifice proportion. Histopathological evaluation of the neck region was performed by light microscopy and scanning electron microscopy.

RESULTS: Fibronectin-coated, ion-implanted coils showed the greatest acute thrombogenicity (average thrombus weight for standard coils, 1.9 ± 1.5 mg; weight for fibronectin-coated coils, 8.6 ± 6.2 mg; $P < 0.0001$). By using scanning electron microscopy, an intensive blood cellular response was observed on ion-implanted coil surfaces, whereas this was rare with standard coils. At Day 14, greater fibrous coverage of the necks of aneurysms was observed in the ion-implanted coil group (mean fibrous membrane to orifice proportion of $69.8 \pm 6.2\%$ for the ion-implanted coil group, compared with $46.8 \pm 15.9\%$ for the standard coil group; $P = 0.0143$).

CONCLUSION: The results of this preliminary experimental study indicate that ion implantation combined with protein coating of GDCs improved cellular adhesion and proliferation. Future application of this technology may provide early wound healing at the necks of embolized, wide-necked, cerebral aneurysms. (Neurosurgery 40:1233-1244, 1997)

Key words: Animal models, Cell adhesion, Cerebral aneurysm, Embolization, Endothelium, Endovascular therapy

Early experience with experimental and clinical use of Guglielmi detachable coils (GDCs) (Target Therapeutics, Fremont, CA) points to their effectiveness in the endovascular occlusion of small-necked intracranial saccular aneurysms (13-15). However, the anatomic results of obliteration of either wide-necked or giant aneurysms by using GDCs are less satisfactory (14, 44). The reasons for these incomplete anatomic results with wide-necked lesions include coil compaction and the potential for distal migration. Early intravascular re-endothelialization at the necks of aneurysms and the acceleration of "wound healing" in the aneurysmal sac and dome are potential solutions that may help achieve successful permanent cures for this type of aneurysm.

Ion implantation is a physicochemical surface modification process resulting from the impingement of a high-energy ion beam (18). When ion implantation is performed, the chemical characteristics of the surface of a material are changed. Therefore, alteration and manipulation of the thrombogenicity and control of the cell-adhesive properties of a material surface might be possible and might be used to one's advantage. Recently, this technology has been applied to the surface modification of polymers, to improve their blood compatibility (37). Ion implantation also increases endothelial cell migration and proliferation on the modified surface (37, 38). Recently, the use of extracellular matrix proteins such as collagen or fibronectin has been attempted as a therapeutic adjunct for promotion of wound healing (5, 31, 32). If ion implantation is performed on a protein-coated platinum surface ("ion bombardment"), the coated protein becomes embedded in the platinum, resulting in a minimal increase in coil diameter and a "mixing" of the protein into the platinum surface. This process may create significant changes in the physicochemical structure of the modified surface of the coils.

It was hypothesized that use of ion-implanted, protein-coated GDCs might be useful for achieving complete obliteration of aneurysms possessing wide necks, by acceleration of re-endothelialization and wound healing. The purpose of this preliminary feasibility study was to investigate the potential effectiveness of these modified GDCs in endovascular treatment of experimental wide-necked aneurysms in swine.

MATERIALS AND METHODS

The overall design of this research focused on two studies, i.e., an acute thrombogenicity study in swine arteries, to compare standard and modified straight platinum coils, and a chronic experimental aneurysm treatment study with standard and modified GDCs, to evaluate their effects on aneurysm healing.

Ion implantation process

Figure 1 schematically shows an ion implantation system that is used for modification of platinum coil surfaces. The processes are typically performed at low temperature under high vacuum. The equipment consists of sections for extraction of ions from the ion source, acceleration of the ions to high energies, mass analysis of ions to select specific ion species, ion-beam raster scanning, beam shaping for distribu-

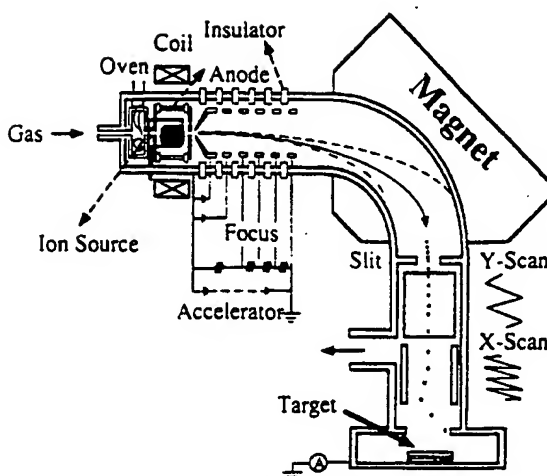


FIGURE 1. Schematic diagram of the ion implantation system (RIKEN 200 kV Ion Implanter) used for modification of platinum coil surfaces.

tion of the energy of the ion beam over large surface areas by electrostatic lens elements, and fixturing in the processing vacuum chamber for manipulation of coils in front of the beam for uniform coverage. Figure 2 schematically demonstrates the ion implantation process applied to a protein-coated platinum surface. After ion implantation, the surface

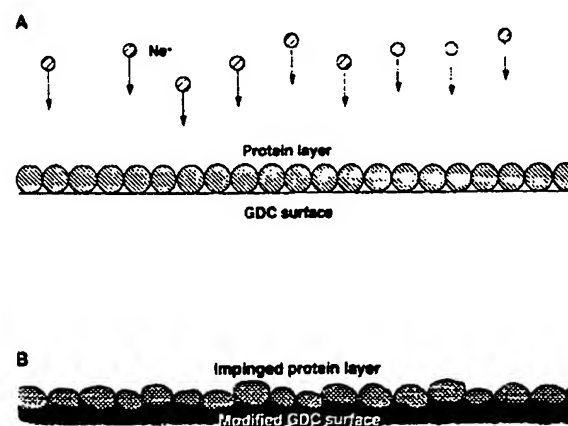


FIGURE 2. Schematic diagram of ion implantation on a protein-coated platinum surface and the resultant changes in surface properties. A, before ion implantation. B, after ion implantation. Note that the surface protein is impinged strongly by the ion beam, resulting in embedding within the platinum surface and alterations of the protein properties.

protein is impinged by the ion beam, resulting in embedding within the platinum surface and altered protein properties.

Assessment of acute thrombogenicity

All animal experimentation was conducted in accordance with policies set by the University of California, Los Angeles, Chancellor's Animal Research Committee and National Institutes of Health guidelines. Seventeen Red Duroc swine were used in this short-term study. The animals were 3 to 4 months old, weighed 30 to 40 kg, were of both genders, and were maintained on a standard laboratory diet. After an overnight fast, each animal was premedicated with intramuscular administration of 20 mg/kg ketamine and 2 mg/kg xylazine. General anesthesia was maintained with mechanical ventilation and inhalation of 0.5 to 1.5% halothane after endotracheal intubation.

The interactions of coils and blood were studied to assess the differences in basic surface properties between standard platinum coils and modified coils (i.e., protein-coated and ion-implanted). Separate straight platinum coils (0.015-inches thick; Target Therapeutics) were each coated with either fibronectin (human plasma fibronectin, 0.5 mg/ml; KOKEN, Tokyo, Japan), type I collagen (bovine dermis collagen, 0.3%; KOKEN), or nonthrombogenic albumin (human serum albumin, 50 mg/ml; Midorijuji, Osaka, Japan). The coating method entailed simply dipping the coils into the protein solutions and drying them for up to 2 hours. These straight coils underwent Ne^+ implantation at a dose of 1×10^{15} ions/cm² and an energy of 150 keV. Straight noncoated and non-ion-implanted platinum coils ("standard coils") were used as controls. Figure 3 shows the scanning electron microscopic surface appearances of a standard coil and a modified coil. After protein coating and ion implantation, the coil thickness was minimally affected. The coils (34 in total; 7 for each of the albumin-coated, fibronectin-coated, and collagen-coated groups and 13 standard coils) were cut so that they were equal in length and weight (length, 22.5 mm; weight, 26.3 ± 0.731 mg; mean \pm standard deviation). Thirty-four common iliac arteries of 17 swine were used in this short-term study. Under general anesthesia, a 6-French angiographic sheath was placed in the each femoral artery. By this transfemoral route, a guiding sheath (Target Therapeutics) normally used for advancing GDCs was navigated coaxially and its tip was positioned in the common iliac artery distal to the iliac bifurcation. The end of each coil was tied with 7-0 prolene, introduced into the common iliac artery by advancement with a coil pusher (Target Therapeutics), and left in place for 1 hour. After 1 hour, each coil and guiding sheath were carefully withdrawn together into the angiographic sheath, under fluoroscopy, and pulled out with the angiographic sheath. These specimens were immediately immersed in saline, fixed with 2.0% glutaraldehyde, and weighed. These specimens were then dehydrated in graded ethanol, coated with gold, and observed at magnifications of $\times 200$ to $\times 2000$, in a scanning electron microscope at an accelerating voltage of 15 kV. Statistical analysis of the weights of thrombus was performed by using the analysis of

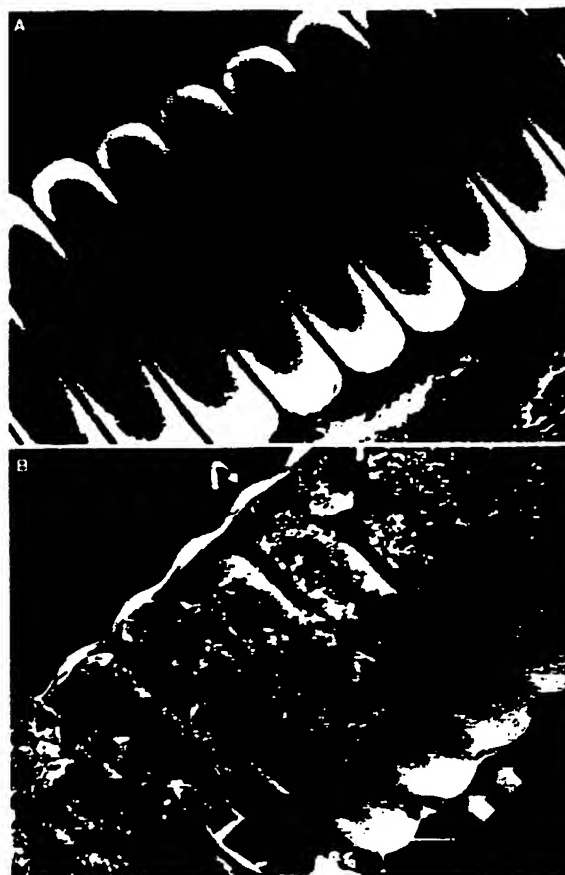


FIGURE 3. Scanning electron-microscopic appearances (original magnification, $\times 200$) of the surface of a standard coil (A) and a coil that was only protein-coated on one half (thick white arrows) and was protein-coated and ion-implanted on one half (thick black arrows) (B). Note that the thickness of protein coating is $\sim 30 \mu m$ (between curved arrows); this diminishes after ion implantation (see Discussion).

variance method. Results were considered significant at $P < 0.05$ and are reported as the mean \pm standard deviation.

Assessment of GDCs in experimental aneurysms

Coil preparation

GDCs of sizes 8×40 , 8×20 , 6×20 , and 5×15 (coil diameter [mm] \times length [cm]) of GDC-18 thickness (i.e., 0.015 inches) and size 4×10 of GDC-10 thickness (i.e., 0.010 inches) were coated with either fibronectin, type I collagen, vitronectin (bovine plasma vitronectin, 0.1 mg/ml; KOKEN), laminin (mouse laminin, 1.0 mg/ml; KOKEN), fibrinogen (human fibrinogen, 20 mg/ml; Midorijuji, Osaka, Japan), or albumin. Ion implantation was then performed with these protein-coated GDCs. The electrical resistance of five standard GDCs,

five ion-implanted GDCs, and five ion-implanted and albumin-coated GDCs were examined by using a standard ohmmeter.

Aneurysm construction

Preoperative preparation of the animals was as described above. Thirty-four experimental aneurysms were constructed microsurgically in bilateral common carotid arteries of an additional 17 swine. The neck of each animal was shaved, scrubbed with betadine solution, and then sterilely draped. Under sterile conditions, a 10-cm incision was made in the midline of the neck. Self-retractors were used to facilitate exposure. By reflecting the right sternocleidomastoid muscle medially, a 4-cm segment of the right external jugular vein was isolated at both ends with a ligature and then divided to form an open-ended vein segment, to be used as the venous graft. This vein was divided into two equal segments to make two aneurysms of equal size. Next, by using a surgical microscope, a 3-cm segment of the right common carotid artery was exposed and cleaned of adventitia. Two small vascular clamps were then placed at each end of the isolated common carotid artery segment to achieve temporary vessel occlusion. A 7-mm-long arteriotomy was carefully performed and a veno-arterial end-to-side anastomosis was made by using 7-0 prolene. This resulted in a uniform neck size (7 mm) for all constructed aneurysms. The second aneurysm was constructed on the left common carotid artery. The aneurysm sacs were almost all of equal size, ranging from 8 to 10 mm (mean, 9.0 ± 0.7 mm) (Fig. 4A). During the procedure, the swine received 0.9 to 1.2×10^6 units of penicillin G intramuscularly.

Aneurysm embolization

All endovascular treatments were undertaken in aneurysms immediately after their construction. Aneurysms maintained chronically (to assess their natural thrombosis or growth rate) before the embolization procedures were not used in this preliminary study. Instead, bilateral aneurysms were embolized in each animal, and the relative differences in wound healing between treatments using ion-implanted and standard GDCs were evaluated. It was thought that any underlying spontaneous growth/thrombosis would be similar in bilateral aneurysms and would have the same effects with both treatments.

A 6-French angiographic sheath was placed in the right femoral artery after standard Seldinger puncture and catheterization. By this transfemoral route, a selective common carotid arteriogram was obtained by using a 6-French Fas-guide catheter (Target Therapeutics), and the aneurysm was outlined in multiple projections. A bolus of 3000 units of heparin was injected to prevent thrombosis during the procedure. Next, a Tracker 18 microcatheter and Seeker 14 microguidewire combination (Target Therapeutics) was advanced coaxially through the guiding catheter, and the tip of the microcatheter was positioned in the center of the aneurysm sac. The aneurysms were embolized with standard GDCs on one side and ion-implanted, protein-coated GDCs on the contralateral side (Fig. 4B). Packing with coils was the

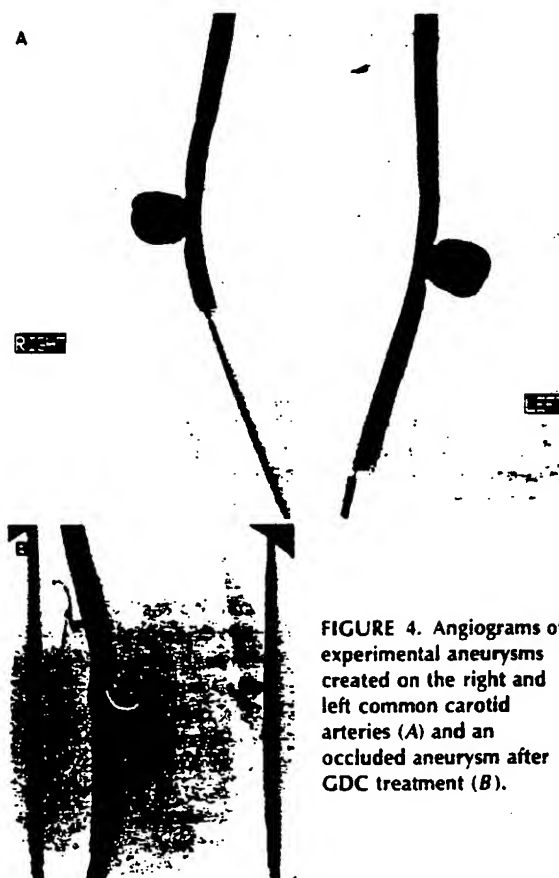


FIGURE 4. Angiograms of experimental aneurysms created on the right and left common carotid arteries (A) and an occluded aneurysm after GDC treatment (B).

goal of treatment for each aneurysm, to reduce the occurrence of persistent unobliterated portions of aneurysms and the effects of consequent hemodynamic inequalities that might affect the migration of endothelial cells across the aneurysm neck. To assume equal packing of different aneurysms with coils, the relative volume of metallic coils in relation to the volume of the aneurysms being embolized was calculated as follows: $\text{total length of the coils used in each aneurysm} \times (\text{coil radius})^2 \times \pi / \text{volume of aneurysm} \times 100\%$. All aneurysms were assumed to be spherical for the purpose of this calculation. There was no statistically significant difference ($P = 0.3542$, paired two-tailed t test) between the ion-implanted GDC group ($17.4 \pm 4.4\%$, $n = 10$) and the standard GDC group ($19.2 \pm 6.2\%$, $n = 10$) at the post-treatment Day 14 evaluation. One aneurysm was not treated and acted as a control (with follow-up monitoring to 60 days after construction). The physical and performance characteristics of the modified GDCs were evaluated during the endovascular procedures.

Diagnostic angiography was performed on Days 7, 14, 21, 30, and 60 after coil placement, after which each animal was euthanized by using standard approved procedures. The parent arteries of specimens were cut lengthwise, and the aneu-

aneurysm orifice (as viewed from within the artery lumen) was observed macroscopically. The largest dimensions of the orifice and the thick white fibrous membrane that covered the orifice were measured as the fibrous membrane to orifice proportion and recorded as fibrous membrane/orifice $\times 100\%$ (Fig. 5). This evaluation was conducted on specimens 14 days after embolization ($n = 10$ for the standard group and $n = 10$ for the ion-implanted, protein-coated group [$n = 2$ with vitronectin, $n = 2$ with collagen, $n = 2$ with laminin, $n = 2$ with fibrinogen, $n = 1$ with albumin, and $n = 1$ with fibronectin]). In this study, particular attention was paid to the extent of fibrous membrane coverage over the aneurysm orifice as a measure of wound healing acceleration. Statistical analysis of the fibrous membrane to orifice ratio was performed by using the Student *t* test (paired two-tail). Results were considered significant at $P < 0.05$ and are reported as the mean \pm standard deviation. Any coverage of the aneurysm neck by a thinner clear membrane was also noted but was not included in the statistical evaluation. The treated aneurysm specimens were fixed with 2% formaldehyde and embedded in plastic resin. Histological sections (20–30- μ m thickness) through the exact midline of the aneurysm orifice (between each stay suture) were obtained by using a diamond knife and then stained with hematoxylin and eosin.

RESULTS

Assessment of acute thrombogenicity

The average weights of thrombus accumulated on straight coils were 1.9 ± 1.4 mg for standard coils, 8.0 ± 5.5 mg for fibronectin-coated coils, 3.9 ± 1.6 mg for collagen-coated coils, and 2.3 ± 1.4 mg for albumin-coated coils. Thrombus accumulated on fibronectin-coated, ion-implanted coils was significantly heavier than that on standard coils ($P < 0.0001$). The weight of thrombus on the albumin- and collagen-coated

coils did not differ significantly from that on standard coils ($P = 0.7720$ for albumin; $P = 0.1420$ for collagen) (Fig. 6). However, an intense blood cellular response (mostly composed of platelets and red blood cells) was observed, by scanning electron microscopy, on all modified coil surfaces except those coated with albumin (Fig. 7A). On the other hand, fibronectin- and collagen-coated, ion-implanted coils demonstrated a strong response. The nonthrombogenic albumin-coated GDCs also showed direct cell adhesion on their surfaces, but this was the least intense. The standard coils demonstrated a different blood cellular response; a layer of protein and fibrin-like substance was deposited between the coil gaps, and blood cell adhesion (mainly of leukocytes) was observed on the fibrin layer (Fig. 7B).

Physical and performance characteristics of modified GDCs

After protein coating alone, the diameter of each GDC increased by ≈ 60 μ m. When these GDCs were further implanted with ions, their diameters were observed to decrease, compared with findings before ion implantation, resulting overall in coils with a minimal increase in diameter (≈ 1 – 10 μ m), compared with standard GDCs (Fig. 3). This reduction in diameter after ion implantation is likely the result of the embedding of some of the protein coating within the platinum surface and the dislodging of some of the protein by the force of the impinging, high-intensity ion beam.

The basic physical characteristics of GDCs, such as their softness, smoothness, and memory shape, were minimally affected by the ion implantation process. There was no unfavorable change in GDC performance (with respect to pushability, softness, and memory shape) during in vivo delivery of the coils with standard microcatheters. Coil detachment times were 87.5 ± 60.6 seconds for standard GDCs and 95.3 ± 58.4 seconds for ion-implanted GDCs ($n = 20$ for each group; $P = 0.6888$, Student *t* test, paired two-tail). No difference in average electric resistance was observed between normal GDCs (0.649 k Ω), ion-implanted GDCs (0.641 k Ω), and ion-implanted, fibronectin-coated GDCs (0.645 k Ω).

Macroscopic and light-microscopic findings for treated aneurysms

The macroscopic and microscopic findings for treated aneurysms are summarized in Table 1. At Day 7 after emboliza-

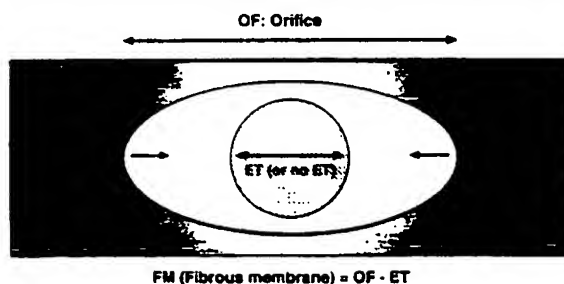


FIGURE 5. Schematic diagram of the method used for evaluating wound healing at the neck of an aneurysm. The largest dimensions of the orifice (OF) of the aneurysm and the white fibrous membrane (FM) that covers the orifice were recorded. These were expressed as the fibrous membrane to orifice proportion (fibrous membrane/orifice $\times 100\%$). The fibrous membrane value was derived from the orifice value minus the value for the thin endothelial membrane over the aneurysm orifice or the uncovered residual aneurysm orifice (ET).

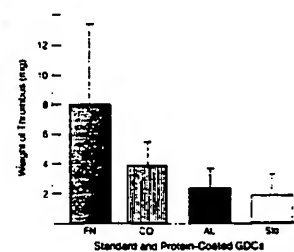


FIGURE 6. Evaluation of acute thrombogenicity of standard and ion-implanted, protein-coated GDCs by comparison of thrombus weights (mean \pm standard deviation) after 1-hour placement in swine iliac arteries. FN, fibronectin ($n = 7$); CO, collagen ($n = 7$); AL, albumin ($n = 7$); Std, standard ($n = 13$).

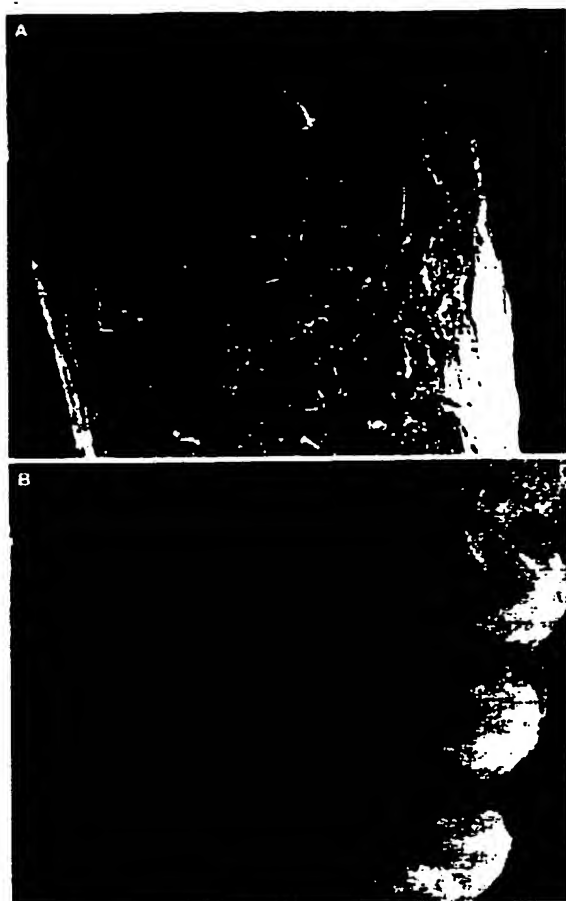


FIGURE 7. Scanning electron micrographs of the surfaces of an ion-implanted, collagen-coated platinum coil (original magnification, $\times 200$) (A) and a standard platinum coil (original magnification, $\times 300$) (B) after 1 hour in swine iliac arteries. Note the intensive blood cellular response on the ion-implanted, protein-coated platinum coil surface.

tion, neither use of standard GDCs nor use of modified GDCs resulted in an endothelium-like thin layer over aneurysm orifices. No clear difference in performance between standard and ion-implanted GDCs could be detected at this stage of follow-up. In specimens examined 14 days after embolization, greater fibrous tissue coverage at the neck of the aneurysm was observed macroscopically (Fig. 8). The mean fibrous membrane to orifice proportion was $69.1 \pm 10.7\%$ for the ion-implanted GDC group and $45.6 \pm 18.0\%$ for the standard GDC group ($P = 0.0035$) (Fig. 9). Light microscopy showed that well-organized fibrous tissue bridged the aneurysmal neck when fibronectin-, vitronectin-, and laminin-coated GDCs were used, whereas only a fibrin-like thin layer covered the standard GDC surfaces (Fig. 10). At Day 21, the necks of aneurysms treated with either standard or coated GDCs were almost all completely covered with a thin membrane. Light

microscopy showed that red blood cells were still observed on standard GDCs and albumin-coated GDCs. At Day 30 of follow-up, the orifices of standard GDC- and ion-implanted GDC-treated aneurysms were completely covered with a thick fibrous membrane, and well-organized fibrous tissue filled all of the aneurysms. Interestingly, the nontreated aneurysm showed enlargement of its sac at day 7. However, it showed shrinkage and partial thrombosis of the sac at Day 21; by Day 60, the nontreated aneurysm was completely thrombosed.

DISCUSSION

Recent advances in endovascular techniques have proved valuable in the treatment of cerebral saccular aneurysms. GDCs have contributed especially to improvements in the endovascular management of cerebral aneurysms. However, the size of an aneurysm neck has an important effect on the anatomic results of aneurysm obliteration. Zubillaga et al. (44) reported that complete obliteration of aneurysms was achieved in 85% of small-necked aneurysms and 15% of wide-necked aneurysms.

GDCs and surrounding thrombus within an aneurysm are continuously exposed to and interact with circulating blood at the neck of the aneurysm. Coil compaction resulting from the force of pulsatile arterial blood flow is one of the reasons for incomplete obliteration of aneurysms. When this occurs, there is a potential risk of aneurysm recanalization and (re)rupture. Re-endothelialization and the promotion of wound healing in the aneurysmal sac and across its neck are necessary for complete aneurysm cure. Despite the many advantages of GDCs in the treatment of aneurysms, several recent clinical and experimental reports have highlighted their potential limitations in achieving an anatomic cure for wide-necked lesions. Molyneux et al. (25) reported two human autopsy cases treated with GDCs for which the long-term (up to 6 mo) histological findings revealed unorganized thrombus in the aneurysms, with no evidence of endothelialization across the aneurysmal neck in either case. Mizoi et al. (24) reported the histological findings for a patient with an anterior communicating artery aneurysm that had been previously treated with GDCs, in whom the compaction of coils resulted in an aneurysm remnant that was subsequently (6 mo later) treated surgically. Histological examination of this resected aneurysm also revealed the presence of unorganized intra-aneurysmal thrombus that was exposed directly to the blood circulation without neointimal formation. Mawad et al. (22) reported a long-term GDC study with experimental canine aneurysms. Their results showed three of nine initially completely embolized aneurysms yielding to subsequent recanalization. Tenjin et al. (40) reported an experimental GDC study in monkey aneurysms. One of four of their cases at 14 days of follow-up showed an aneurysmal "shoulder," indicative of aneurysm recanalization. More recently, Spetzger et al. (35), by using experimental bifurcation aneurysms in rabbits, demonstrated the absence of organized thrombus and no neck endothelialization in treated aneurysms, even after follow-up periods of 3 to 6 months. These results suggest that modification of GDC

TABLE 1. Summary of Results of Coil Treatment of Swine Aneurysms^a

Day	Coil	n	Macroscopic Findings	Microscopic Findings	FML/OF Proportion (%)
0	Standard	1	No membrane over orifice	RBC, unorganized clot	0
	Fibronectin	1	No membrane over orifice	RBC, unorganized clot	0
	Standard	2	Complete thrombosis, thin membrane -	RBC, fibroblasts, unorganized clot	0
	Albumin	1	Partial clot formation	RBC, fibroblasts, unorganized clot	0
	Fibronectin	1	Complete thrombosis, thin membrane --	RBC, fibroblasts, fibrous tissue in the dome	0
14	Standard	10	Thin membrane ---, coil partially exposed	Fibrin-like thin layer on the coils, partial unorganized clot	48
	Fibronectin	1	Thin membrane +---, smooth thick membrane	Fibrous layer on the coils, organized fibrous tissue in the dome	80
	Vitronectin	2	Thin membrane +---, thick membrane	Fibrous layer on the coils, organized fibrous tissue in the dome	66
	Laminin	2	Thin membrane +---, thick membrane	Fibrous layer on the coils, organized fibrous tissue in the dome	71
	Collagen	2	Thin membrane +---, partially thick membrane	Partial fibrous layer at the neck, organized fibrous tissue in the dome	74
	Albumin	1	Thin membrane ++, coil partially exposed	Fibrin-like thin layer at the neck, partial unorganized clot	50
	Fibrinogen	2	Thin membrane +---, irregular thick membrane	Well-organized fibrous tissue	71
21	Standard	1	Thin membrane +---, thick membrane	Fibrous layer at the neck, partial unorganized clot	100
	Albumin	1	Thin membrane +---, thick membrane	Fibrous layer at the neck, partial unorganized clot	80
30	Standard	2	Thick membrane over orifice	Thick fibrous layer at the neck, organized clot	100
	Albumin	1	Thick membrane over orifice	Thick fibrous layer at the neck, organized clot	100
	Fibronectin	1	Thick membrane over orifice	Thick fibrous layer at the neck, organized fibrous tissue in the dome	100
60	Standard	1	Thick membrane over orifice	Well-organized fibrous tissue in the aneurysm	100
	No coil	1	Thick membrane over orifice	None	100

^a ≤25% thin membrane coverage at the orifice; ++, between 26 and 50% thin membrane coverage at the orifice; +---, between 51 and 75% thin membrane coverage at the orifice; +---, complete thin membrane over the orifice; RBC, red blood cells; FM/OF, fibrous membrane/orifice.

performance would be desirable to achieve earlier re-endothelialization and promotion of fibrosis of wide-necked or giant aneurysms than is currently possible.

It is necessary to increase thrombogenicity in preparation for acceleration of wound healing. Coil thrombogenicity was enhanced previously by increasing the surface area of the coils with fabric strands, such as Dacron, and by placing such coils into a thrombin solution (23). More recently, some investigators have modified the surfaces of platinum coils by coating them with collagen or polyurethane (1, 6, 20). This has resulted in some advantages, such as an increase in thrombogenicity of these coils. However, protein coatings on platinum surfaces are usually weak and may be removed easily during the delivery of the coils. Additionally, weakly coated proteins may be washed off by high-velocity arterial flow and may be a potential source of distal thromboemboli. There is also the potential problem of increases in the diameters of these coils;

polyurethane coatings in particular also have the disadvantage of producing unfavorable changes in GDC performance, affecting their softness, thinness, smoothness, and memory shape.

Ion implantation

Ion implantation itself does not provide a coating for coils. It is a surface modification process that uses the impingement of a high-energy ion beam onto the surface of coils to modify their surface properties. This technology has been used to improve the surface properties of metals, e.g., to increase the wear and corrosion resistance of surfaces of artificial hip joints (33). Recently, Suzuki et al. (36-38) applied this process to the modification of polymer surfaces to achieve blood compatibility. There are many advantages to ion implantation, including the following: 1) it is a surface modification process that

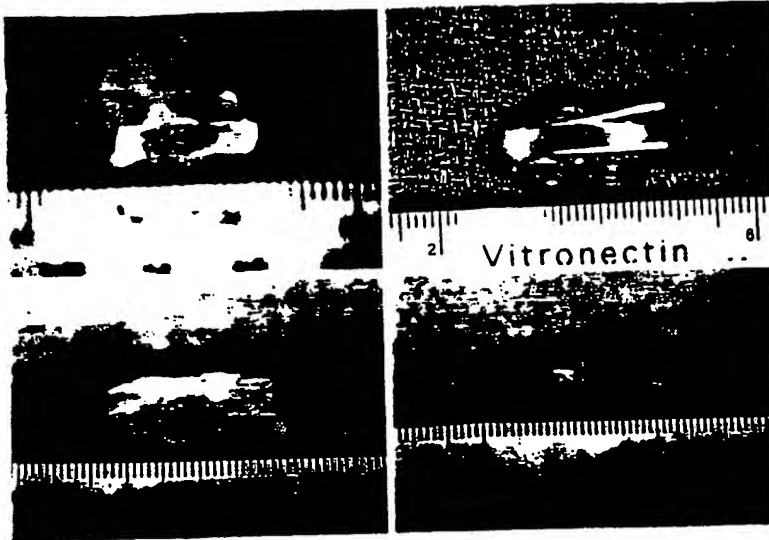


FIGURE 8. Macroscopic appearances of aneurysm orifices 14 days after treatment, with standard GDCs (top left), vitronectin-coated, ion-implanted GDCs (top right), fibronectin-coated, ion-implanted GDCs (bottom left), and laminin-coated, ion-implanted GDCs (bottom right).

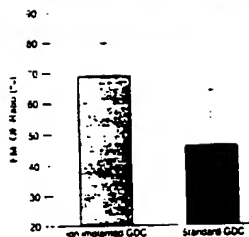


FIGURE 9. Statistical analysis of fibrous membrane (FM) to orifice (OF) ratios for treated aneurysms at Day 14. Standard GDC group (n = 10), 45.6 ± 18.0%; ion-implanted GDC group (n = 10), 69.1 ± 10.7% (P = 0.0035, paired two-tail test).

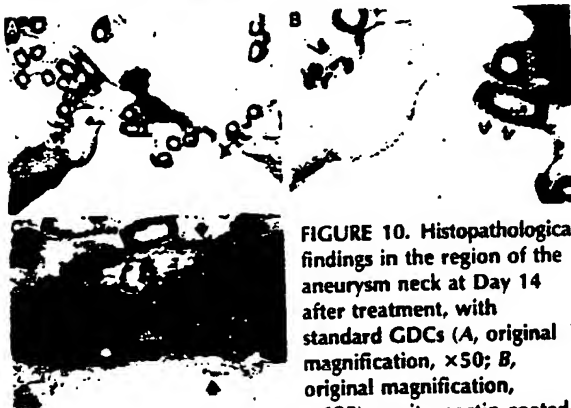


FIGURE 10. Histopathological findings in the region of the aneurysm neck at Day 14 after treatment, with standard GDCs (A, original magnification, x50; B, original magnification, x125) or vitronectin-coated, ion-implanted GDCs (C, original magnification, x100). Note the intensive fibrous response (arrows) with the ion-implanted, protein-coated GDCs. Only a thin fibrin layer (curved arrows) was observed at the aneurysm neck treated with the standard GDCs.

enhances the biochemical properties of the substance that is treated; 2) it causes minimal changes in the diameter of the substance that is treated and covering proteins become embedded in the material surface, resulting in an overall increase

in diameter of approximately 1 to 10 μm ; 3) the basic physical properties and performance characteristics of the platinum coils are minimally affected; 4) it increases endothelial cell migration and proliferation on the modified surface; 5) it enhances cell adhesion onto surfaces by mixing effects on the cell-adhesive proteins; 6) it is a highly controllable and reproducible process that provides uniform impurity doping on substrate planes, accurate fluence, and well-controlled depth distribution within the substance undergoing ion implantation; and 7) there exist a large number of ion species to choose from in the targeting of material surfaces. In this study, we used a Ne^+ beam at a dose of 1×10^{15} ions/ cm^2 and an energy of 150 keV. Determination of the optimal ion species and ion dose for implantation of platinum coils remains under investigation.

Protein coatings of platinum coil surfaces

To achieve strong cellular adhesion and to promote wound healing in aneurysms, we combined the process of ion implantation with various protein coatings on the surfaces of platinum coils. Fibronectin is a noncollagenous extracellular matrix glycoprotein that promotes cell adhesion and migration. Fibronectin plays an important role in tissue repair, showing molecular affinities for collagen, hyaluronic acid, and fibrin, which are major components of early wounds. It is a chemotactic glycoprotein for fibroblasts, smooth muscle cells, and endothelial cells (3, 10, 12, 17, 26). Type I collagen also promotes the migration of fibroblasts (10, 29, 30). Recently, Futami et al. (9) reported that Types I and IV collagen and fibronectin in the subendothelial space were deficient in hypertension-induced experimental aneurysms. Austin et al. (2) investigated the distribution of fibronectin and Type I collagen in human aneurysms and parent arteries and found that Type I collagen was restricted to the outer adventitial region, whereas fibronectin seemed to be limited to the medial layer surrounding smooth muscle cells. These studies suggest that fibronectin may play an important role in the natural repair mechanisms of aneurysms. Furthermore, some investigators have reported that plasma fibronectin increases with age, and they have speculated that this increase might be a compensatory mechanism resulting from a decrease in the biological activity of fibronectin produced by older endothelial cells (19, 39). This suggests that appropriate replacement therapy (at least localized to the sites of aneurysms) of fi-

bronectin might be advantageous. Laminin and vitronectin also play important roles in cell attachment and wound healing. Vitronectin promotes the attachment and spreading of a wide variety of cell types (e.g., fibroblasts, endothelial cells, platelets, and carcinoma cells) (7, 29). Vitronectin attachment-promoting activities in plasma and serum prepared for cell culture are greater than those of fibronectin (16, 41). Laminin is a major basement membrane component and binds cells, such as smooth muscle cells and endothelial cells, to their surrounding Type IV collagen (4, 8, 42). It plays an important role in nerve growth and repair, and recently it has been implicated in tumor metastasis (4, 21, 43). During blood coagulation and wound healing, fibrinogen polymerizes to form a fibrin matrix, providing a substratum over which connective tissue cells migrate and proliferate. A recent study has shown that the constituent chains of fibrinogen not only provide this substratum but also promote fibroblast proliferation (11). All of these cell-adhesive proteins have common binding sites (the Arg-Gly-Asp sequence), which are recognized by receptors on various cell types, including platelets, fibroblasts, and endothelial cells, and have the potential for various therapeutic applications (34).

In this preliminary study, ion-implanted, protein-coated GDCs (except those coated with albumin) resulted in enhanced acceleration of wound healing at the necks of aneurysms. We compared only ion-implanted, protein-coated GDCs and standard GDCs. It is unclear at this stage what the relative contributions of these two processes (ion implantation and protein coating of coils) might be in altering the surface properties of GDCs. The results of this preliminary feasibility study demonstrate that the combination of the two processes can change the behavior of coils when certain surface proteins are used. However, it remains to be determined in future studies how ion-implanted GDCs without protein coatings or protein-coated GDCs without implanted ions would behave under similar conditions in experimental aneurysms. The optimal single coating (or best combination of these proteins) to achieve the most effective wound healing is also under investigation.

Modified GDC performance

The attractive features of GDCs, such as their softness, thinness, and fine memory shape, should be preserved, because these properties are necessary for safe and effective aneurysm treatment. The modified GDCs in this study did not show unfavorable changes in these characteristics during the embolization procedure.

Wound healing with use of modified GDCs

Our study investigating acute thrombogenicity of modified coils showed an intense blood cellular response on ion-implanted and protein-coated coil surfaces. Interestingly, although albumin is known to be a nonthrombogenic protein, the ion implantation process transformed the albumin-coated surface to a thrombogenic one. Fibronectin- and collagen-coated coils demonstrated a strong cellular response when their surfaces underwent ion implantation. Under these

circumstances, the resulting thrombus appeared firm and stable, which may help in reducing the potential for distal thromboembolization.

The acceleration of wound healing was observed in aneurysms after use of GDCs modified with fibronectin, vitronectin, or laminin, at Day 14 of follow-up. The histopathological differences in thrombus formation between modified GDCs and standard GDCs were not so obvious within the aneurysmal sac; thrombus formation seemed to accelerate in the aneurysm sac after blood flow was reduced by embolization with either type of GDCs. On the other hand, thrombus formation was less pronounced in the region of the aneurysm neck, because of the constant exposure to high arterial blood flow. Given these hemodynamic conditions at the aneurysm neck, the standard platinum surface proved to be too smooth for cellular attachment, but the modified GDCs, especially those coated with vitronectin, fibronectin, or laminin, showed acceleration of wound healing. However, the optimal cell-adhesive protein for this purpose remains under investigation.

With respect to the results of this preliminary study, it is unclear how similarly embolized human intracranial aneurysms would behave histopathologically if protein-coated, ion-implanted coils were positioned across their necks. It is known, at least, that the coagulation properties of swine blood are similar to those of human blood (27). However, it is acknowledged that the relatively early (after 14 days of treatment) assessment of the wound healing properties of modified GDCs in young healthy laboratory swine (which may have an underlying strong natural tendency for wound healing) represents a general limitation of this study. Moreover, the presence of natural wound healing at the surgical incision is acknowledged to be an additional factor that might have influenced our observations of neck coverage. This is further highlighted by the natural thrombosis and complete wound healing of the single aneurysm monitored for 60 days without embolization.

Our eventual goal is to produce modified GDCs with which the basic GDC performance is unchanged but the additional benefit of strong promotion of endothelialization is observed. Importantly, the promotion of excessive thrombogenesis must be avoided. With ion implantation, the adhesion of platelets to surfaces begins after the use of an ion beam intensity of 1×10^{14} ions/cm², whereas endothelial cell adhesion properties commence after use of an ion beam intensity of 1×10^{15} ions/cm² (Y Suzuki, unpublished observations). Thus, achievement of strong cell adhesion with a nonthrombogenic surface remains an important goal that is currently under investigation.

CONCLUSION

A preliminary feasibility study was conducted to evaluate the performance of ion-implanted, protein-coated GDCs in the treatment of experimental swine aneurysms. The blood cellular response was enhanced with these modified coils. However, a statistically significant increase in thrombus formation was achieved only for ion-implanted, fibronectin-coated coils. There were no unfavorable changes in the basic GDC physical and performance characteristics. Modified

GDCs showed significant acceleration of wound healing at the necks of aneurysms. We think that imparting this type of modified surface to endovascular devices might lead to new possibilities in the treatment of many cerebrovascular diseases. Further investigations will be necessary before clinical application.

ACKNOWLEDGMENTS

We gratefully acknowledge the technical assistance of John Robert and Christopher Carangi of the Leo G. Rigler Radiological Research Center at the University of California, Los Angeles.

Received, October 24, 1996.

Accepted, January 18, 1997.

Reprint requests: Yuichi Murayama, M.D., Endovascular Therapy Service, Department of Radiological Sciences, University of California, Los Angeles, Medical Center, 10833 Le Conte Avenue, Los Angeles, CA 90024.

REFERENCES

- Ahuja AA, Hergenrother RW, Strother CM, Rappe AA, Cooper SL, Graves VB: Platinum coil coatings to increase thrombogenicity: A preliminary study in rabbits. *AJNR Am J Neuroradiol* 14:794-798, 1993.
- Austin G, Fisher S, Dickson D, Anderson D, Richardson S: The significance of the extracellular matrix in intracranial aneurysms. *Ann Clin Lab Sci* 23:97-105, 1993.
- Brothie H, Wakefield D: Fibronectin: Structure, function and significance in wound healing. *Australas J Dermatol* 31:47-56, 1990.
- Campbell JH, Terranova VP: Laminin: Molecular organization and biological function. *J Oral Pathol* 17:309-323, 1988.
- Chvapil M, Kronenthal RL, van Winkle W Jr: Medical and surgical applications of collagen. *Invest Rev Connect Tissue Res* 6:1-61, 1973.
- Dawson RC, Krisht AF, Barrow DL, Joseph GJ, Shengelaia GG, Bonner G: Treatment of experimental aneurysms using collagen-coated microcoils. *Neurosurgery* 36:133-140, 1995.
- Felding-Habermann B, Cheresch DA: Vitronectin and its receptors. *Curr Opin Cell Biol* 5:864-868, 1993.
- Foidart JM, Bere EW Jr, Yaar M, Rennard SI, Gullino M, Martin GR, Katz SI: Distribution and immunoelectron microscopic localization of laminin, a noncollagenous basement membrane glycoprotein. *Lab Invest* 42:336-342, 1980.
- Futami K, Yamashita J, Tachibana O, Higashi S, Ikeda K, Yamashita T: Immunohistochemical alterations of fibronectin during the formation and proliferative repair of experimental cerebral aneurysms in rats. *Stroke* 26:1659-1664, 1995.
- Gauss-Müller V, Kleinman HK, Martin GR, Schiffmann E: Role of attachment factors and attractants in fibroblast chemotaxis. *J Lab Clin Med* 96:1071-1079, 1980.
- Gray AJ, Bishop JE, Reeves JT, Lauent G: $\alpha\beta$ chains of fibrinogen stimulate proliferation of human fibroblasts. *J Cell Sci* 104:409-413, 1993.
- Grinnell F, Feld M, Minter D: Fibroblast adhesion to fibrinogen and fibrin substrata: Requirement for cold-insoluble globulin (plasma fibronectin). *Cell* 19:517-525, 1980.
- Guglielmi G, Vinuela F, Dion J, Duckwiler G: Electrothrombosis of saccular aneurysms via endovascular approach: Part 2—Preliminary clinical experience. *J Neurosurg* 75:8-14, 1991.
- Guglielmi G, Vinuela F, Duckwiler G, Dion J, Lvyk P, Hopkins LN, Ferguson R, Sepetka I: Endovascular treatment of posterior circulation aneurysms by electrothrombosis using electrically detachable coils. *J Neurosurg* 77:515-524, 1992.
- Guglielmi G, Vinuela F, Sepetka I, Macellari V: Electrothrombosis of saccular aneurysms via endovascular approach: Part 1—Electrochemical basis, technique, and experimental results. *J Neurosurg* 75:1-7, 1991.
- Hayman EG, Pierschbacher MD, Suzuki S, Ruoslahti E: Vitronectin: A major cell attachment-promoting protein in fetal bovine serum. *Exp Cell Res* 160:245-258, 1985.
- Hedin U, Bottger BA, Forsberg E, Johansson S, Thyberg J: Diverse effects of fibronectin and laminin on phenotypic properties of cultured arterial smooth muscle cells. *J Cell Biol* 107:307-319, 1988.
- Iwaki M: Formation of metal surface layers with high performance by ion implantation. *Nucl Instr Methods B* 37/38:661-666, 1989.
- Kumazaki T, Kobayashi M, Mitsui Y: Enhanced expression of fibronectin during in vivo cellular aging of human vascular endothelial cells and skin fibroblasts. *Exp Cell Res* 205:396-402, 1993.
- Kwan ESK, Heilman CB, Roth PA: Endovascular packing of carotid bifurcation aneurysms with polyester fiber-coated platinum coils in a rabbit model. *AJNR Am J Neuroradiol* 14:323-333, 1993.
- Liesi P: Extracellular matrix and neuronal movement. *Experientia* 46:900-907, 1990.
- Mawad ME, Mawad JK, Cartwright J Jr, Gokaslan Z: Long-term histopathologic changes in canine aneurysms embolized with Guglielmi detachable coils. *AJNR Am J Neuroradiol* 16:7-13, 1995.
- McLean GK, Stein EJ, Burke DR, Meranze SG: Steel occlusion coils: Pretreatment with thrombin. *Radiology* 158:549-550, 1986.
- Mizoi K, Yoshimoto T, Takahashi A, Nagamine Y: A pitfall in the surgery of a recurrent aneurysm after coil embolization and its histological observation: Technical case report. *Neurosurgery* 39:65-69, 1996.
- Molyneux AJ, Ellison DW, Morris J, Byrne JV: Histological findings in giant aneurysms treated with Guglielmi detachable coils: Report of two cases with autopsy correlation. *J Neurosurg* 83:129-132, 1995.
- Mosher DF: Fibronectin. *Prog Hemost Thromb* 5:111-151, 1980.
- Osterman FA, Bell WR, Montali RJ, Novak GR, White RI Jr: Natural history of autologous blood clot embolization in swine. *Invest Radiol* 11:267-276, 1976.
- Preissner KT: Structure and biological role of vitronectin. *Annu Rev Cell Biol* 7:275-310, 1991.
- Ross R: The fibroblast and wound repair. *Biol Rev* 43:51-96, 1968.
- Ross R: Wound healing. *Sci Am* 220:40-50, 1969.
- San-Galli F, Darrouet V, Rivel J, Baquay C, Ducassou D, Guérin J: Experimental evaluation of a collagen-coated vicryl mesh as a dural substitute. *Neurosurgery* 30:396-401, 1992.
- Scheel G, Rahfoth B, Franke J, Grau P: Acceleration of wound healing by local application of fibronectin. *Arch Orthop Trauma Surg* 110:284-287, 1991.
- Sioshansi P: Medical application of ion beam processes. *Nucl Instr Methods B* 19/20:204-208, 1987.
- Sonnenberg A: Integrins and their ligands. *Curr Top Microbiol Immunol* 184:7-35, 1993.
- Spetzger U, Reul J, Weis J, Bertalanffy H, Thron A, Gilsbach JM: Microsurgically produced bifurcation aneurysms in a rabbit model for endovascular embolization. *J Neurosurg* 85:488-495, 1996.

36. Suzuki Y, Kusakabe M, Akiba H, Kusakabe K, Iwaki M: In vivo evaluation of antithrombogenicity for ion implanted silicone rubber using indium-111-tropolone platelets. *Nucl Instr Methods B* 59: 693-704, 1991.
37. Suzuki Y, Kusakabe M, Kaibara M, Iwaki M, Sasabe H, Nishisaka T: Cell adhesion control by ion implantation into extra-cellular matrix. *Nucl Instr Methods B* 91:588-592, 1994.
38. Suzuki Y, Kusakabe M, Lee JS, Kaibara M, Iwaki M, Sasabe H: Endothelial cell adhesion to ion implanted polymers. *Nucl Instr Methods B* 65:142-147, 1992.
39. Takasaki I, Takizawa T, Sugimoto K, Gotoh E, Shionori H, Ishii M: Effects of hypertension and aging on fibronectin expression in aorta of Dahl salt-sensitive rats. *Am J Physiol* 267:H1523-H1529, 1994.
40. Tenjin H, Fushiki S, Nakahara Y, Masaki H, Matsuo T, Johnson CM, Ueda S: Effect of detachable coils on experimental carotid artery aneurysms in primates. *Stroke* 26:2075-2080, 1995.
41. Tomasini BR, Mosher DF: Vitronectin. *Prog Hemost Thromb* 10:269-305, 1991.
42. Trygghvason K: The laminin family. *Curr Opin Cell Biol* 5:877-882, 1993.
43. Yoshii S, Yamamuro T, Ito S, Hayashi M: In vivo guidance of regenerating nerve by laminin-coated filaments. *Exp Neurol* 96: 469-473, 1987.
44. Zubillaga AF, Guglielmi G, Viñuela F, Duckwiler GR: Endovascular occlusion of intracranial aneurysms with electrically detachable coils: Correlation of aneurysm neck size and treatment results. *AJNR Am J Neuroradiol* 15:815-820, 1994.

COMMENTS

Murayama et al. present their preliminary results in swine model aneurysms treated with ion-implanted, protein-coated Guglielmi detachable coils (GDCs). The results described are very promising. Such developmental attempts may increase the effectiveness of GDC treatment, although, in our opinion, they do not represent an ultimate solution.

The article concentrates on increased coil thrombogenicity. Although improved thrombogenicity is important, we consider hemodynamic changes in the aneurysm and around the aneurysmal orifice to be of greater importance for aneurysm obliteration. Even highly thrombogenic coils cannot effect complete aneurysm occlusion if the packing, especially in the neck region, is insufficient. In our study with collagen-filled GDCs, packing density was the single determinant of aneurysm occlusion (2). Furthermore, improved acute thrombogenicity may increase thromboembolic complications if some of the coil loops protrude toward the parent vessel lumen. Heparin can be administered prophylactically but with the sacrifice of any advantage gained by the improved thrombogenicity.

We think that improved and, more importantly, safer thrombosis can be achieved by altering the hemodynamics near the aneurysm orifice to decrease or halt intra-aneurysmal flow. This flow modification could be achieved by the deployment of well-designed stents or other devices that partially or fully cover the aneurysmal orifice. A combination of stent application and other intravascular methods could also be helpful. Current research efforts are focused on the development of intracranial devices for this purpose.

The animal model used and the lack of nontreated control aneurysms are major limitations of this study. The authors

claim that the coagulation properties of swine blood are similar to those of human blood and thus pigs are ideal subjects for thrombogenicity studies. However, the authors measured the effectiveness of coil treatments as the absence or presence of fibrous tissue coverage at the aneurysm orifice, which is related to wound healing rather than to coagulation. Only one nontreated aneurysm was used as a control lesion in the 60-day post-treatment group, and no control lesions were included in the most important 14-day group. At 60 days, the control aneurysm was completely thrombosed, "with a thick membrane over the orifice" (Table 1). Vein-graft aneurysms in swine tend to occlude spontaneously (1). We now conduct our aneurysm research in a canine model, having produced more than 100 side-wall aneurysms on carotid arteries in dogs, with patencies of more than 90% after 3 months. In addition, we have maintained four dogs with patent aneurysms in our laboratory since 1992, for a long-term follow-up study.

Protein coating and ion implantation may considerably increase the price of the GDC system. Further investigation is necessary before this new technique is used in clinical practice.

László Miskolczi
L. Nelson Hopkins
Buffalo, New York

1. Chavis TD, Wakhloo AK, Szikora I, Standard SC, Guterman LR, Hopkins LN: Evaluation of experimental carotid lateral wall aneurysm model in swine. Presented at the 32nd Annual Meeting of the American Society of Neuroradiology, Nashville, Tennessee, May 1994.
2. Szikora I, Wakhloo AK, Guterman LR, Chavis TD, Dawson RC, Hergenrother RW, Twyford RH, Hopkins LN: Initial experience with collagen-filled Guglielmi detachable coils for endovascular treatment of experimental aneurysms. *Am J Neuroradiol* (in press).

This article gives a fascinating description of a modification of GDCs to increase their thrombogenicity. The use of GDCs in wide-necked aneurysms is imperfect because of the high frequency with which there is either growth of the neck of the aneurysm, migration of coils further into the dome of the aneurysm or clot (if that is present), or compaction of the coils. By increasing the thrombogenicity of the coils, the authors have been able to demonstrate in this animal model that there are changes in the way thrombus forms within the coil mass. Whether these changes will ultimately yield improved results is yet to be demonstrated. One of the major complications of treating wide-necked aneurysms is errant emboli forming at the base of the coils, breaking off, and entering distal normal blood vessels. Whether this type of coating will worsen those types of complications to a degree that negates the benefit of increased thrombogenicity remains to be seen. However, work like this is extremely interesting and should be pursued.

Stanley L. Barnwell
Portland, Oregon

This important contribution attempts to evaluate the performance of modified GDCs for the treatment of experimental

aneurysms in swine. An additional goal of this study was to establish a way to increase the occlusion stability of GDC-treated human cerebral aneurysms.

The experimental system to compare wound healing at the necks of aneurysms packed with modified GDCs and those packed with standard GDCs is reasonable, even if the assumption of "equal packing of different aneurysms with coils" is uncertain. For the purpose of volume calculation and calculation of necessary coil length, the authors assumed their experimental aneurysms to be spherical. Calculated equal packing would presuppose aneurysms equal in size and shape packed with coils equal in number and size; the amount of packing depends not only on the aneurysm volume but also on the choice of helix size and length. On the other hand, it can be assumed that the authors packed their small-neck aneurysms as shown in Figure 4B, avoiding loosely packed zones in the neck area.

The findings on wound healing at the neck level and the calculations of neck occlusion ratios are valid only for the type of experimental aneurysms presented in this study. The aneurysms used here are lateral aneurysms only minimally exposed to the flow; only one aneurysm was left open as a control lesion, and this aneurysm thrombosed spontaneously after 60 days. The aneurysms were packed immediately after their surgical construction. The authors themselves state that "natural wound healing at the surgical incision" and the "strong natural tendency for wound healing" in swine represent general limitations of this study. This is also illustrated by the observation that not only the aneurysms treated with modified coils but also those treated with standard coils showed excellent wound healing tendencies. After 21 days, the aneurysms treated with standard coils showed 100% healing of their aneurysm necks. After 30 days, the "standard GDC"-treated aneurysms all showed thick and well-organized fibrin tissue covering the neck orifice.

This observation is certainly specific for these experimental aneurysms. It is known (and mentioned by the authors) that (even densely packed) human aneurysms treated with GDCs show, after some weeks or months, well-organized thrombus only rarely. They mostly contain nonorganized thrombus or only coils with nothing between them. There is no observation or report of any endothelialized layer or membrane covering the necks of human aneurysms.

From the quick and effective wound healing of the experimental aneurysms treated with standard GDCs, one cannot draw any conclusions regarding potential behavior of the modified coils in human cerebral aneurysms. The coagulation properties of swine blood being similar to those of human

blood cannot be taken as an argument. The experimental rabbit aneurysm model proposed by Spetzger et al. (1) fulfills the criterion of hemodynamic exposure and has wound healing properties more similar to those of human subjects. It would be interesting to obtain information about the differences in wound healing with standard or modified GDCs in that aneurysm model.

Nevertheless, this article deals with the important issue of improvement of endovascular tools for the treatment of cerebral aneurysms. The value of standard GDCs for long-term stability of neck occlusion, especially in aneurysms with necks larger than 4 mm, is so questionable that efforts to improve occlusion stability must be greatly appreciated. In this context, the authors are urged to continue their investigations to approach our common goal of improving endovascular tools for the treatment of cerebral aneurysms.

Bert Richling
Vienna, Austria

-
1. Spetzger U, Reul J, Weis J, Bertalanffy H, Thron A, Gilsbach JM: Microsurgically produced bifurcation aneurysms in a rabbit model for endovascular embolization. *J Neurosurg* 85:488-495, 1996.

The report by Murayama et al. on ion implantation and protein coating of detachable coils for endovascular treatment of cerebral aneurysms is interesting. The obvious problem with any device deployed within an aneurysmal sac is control of the inflow zone. Increasing thrombogenicity might not solve that problem, although it might cause thrombosis within the fundus and the bulk of the aneurysmal complex. As the authors mention, increasing thrombogenicity undoubtedly will increase problems with thromboembolic events, which were difficulties early in the experience with GDCs and which continue to be a serious concern.

I think it is important to recognize that, in their study and in similar studies, there was histological evidence of a fibrous membrane and scar tissue covering the neck of the aneurysm. I think implanting these devices with agents that promote a cellular response is ingenious and certainly deserves further attention. Clearly, with any endovascular device (whether a new type of coil or endoaneurysmal or endovascular stenting), control of the inflow zone is of paramount importance for maintaining obliteration of the lesion.

Robert H. Rosenwasser
Philadelphia, Pennsylvania

We claim:

1. An apparatus for forming a thrombus comprising:
a separable coil comprised at least in part of at least one biocompatible and absorbable polymer or protein; and
a placement device associated with said separable coil adapted to dispose said coil into a selected body lumen.
2. The apparatus of claim 1 wherein said coil further is comprised at least in part of a growth factor.
3. The apparatus of claim 2 wherein said coil further is comprised at least in part of a vascular endothelial growth factor.
4. The apparatus of claim 2 wherein said coil further is comprised at least in part of a basic fibroblast growth factor.
5. The apparatus of claim 3 wherein said coil further is comprised at least in part of a mixture of said vascular endothelial growth factor and a basic fibroblast growth factor.
6. The apparatus of claim 1 wherein said biocompatible and absorbable polymer is at least one polymer selected from the group consisting of polyglycolic acid, poly-D-glycolic acid/poly-L-lactic acid copolymers,

polycaprolactive, polyhydroxybutyrate/hydroxyvalerate copolymers, poly-L-lactide, polydioxanone, polycarbonates, and polyanhydrides.

7. The apparatus of claim 1 wherein said biocompatible and absorbable protein is at least one protein selected from the group consisting of collagen, fibrinogen, fibronectin, vitronectin, laminin, and gelatin.

8. The apparatus of claim 1 wherein said coil is composed of said biocompatible and absorbable polymer or protein, and wherein a radio-opaque material is disposed thereon.

9. The apparatus of claim 1 wherein said coil composed of a radio-opaque material, and wherein said biocompatible and absorbable polymer or protein is disposed thereon.

10. A method for forming a thrombus comprising:
providing a separable coil comprised at least in part of at least one biocompatible and absorbable polymer or protein; and
disposing said separable coil into a body lumen.

11. The method of claim 10 further providing said coil with a growth factor.

12. The method of claim 11 wherein providing said coil with a growth factor comprises providing said coil with a vascular endothelial growth factor.

13. The method of claim 11 wherein providing said coil with a growth factor comprises providing said coil with a basic fibroblast growth factor.

14. The method of claim 12 wherein providing said coil with a growth factor comprises providing said coil with a mixture of said vascular endothelial growth factor and a basic fibroblast growth factor.

15. The method of claim 10 wherein providing said separable coil comprised with said biocompatible and absorbable polymer comprises providing said coil with at least one polymer selected from the group consisting of polyglycolic acid, poly-glycolic acid/poly-L-lactic acid copolymers, polycaprolactone, polyhydroxybutyrate/hydroxyvalerate copolymers, poly-L-lactide, polydioxanone, polycarbonates, and polyanhydrides.

16. The method of claim 10 wherein providing said separable coil comprised with said biocompatible and absorbable protein comprising providing at least one protein selected from the group consisting of collagen, fibrinogen, fibronectin, vitronectin, laminin, and gelatin.

17. The method of claim 10 wherein providing said coil provides a coil composed of said biocompatible and absorbable polymer or protein with a radio-opaque material is disposed thereon.

18. The method of claim 10 wherein providing said coil provides a coil composed of a radio-opaque material with said biocompatible and absorbable polymer or protein is disposed thereon.

INTERNATIONAL SEARCH REPORT

international application No.
PCT/US99/01790

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61F 2/06

US CL : 623/1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 428/410; 514/44; 606/198; 623/1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,549,624 A (MIRIGIAN et al) 27 August 1996, col. 2, lines 17-50.	1, 10
Y,P	US 5,830,879 A (ISNER) 03 November 1998, col. 2, lines 29-36.	2-9, 11-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

29 JUNE 1999

Date of mailing of the international search report

28 JUL 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MATTHEW KISER

Telephone No. (703) 308-5512

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.